Utah Medicaid Pharmacy & Therapeutics Committee

Drug Class Review: Combination Opioid Products

Analgesic Combination Opioid; 28:08.04.92; Opiate Agonists 28:08.08; Centrally Acting Skeletal Muscle Relaxants 12:20.04; Other Nonsteroidal Anti-inflammatory Agents 28:08.92

Codeine + Acetaminophen
(*Capital® and Codeine, Tylenol® with Codeine No. 3, Tylenol® with Codeine No. 4, generic*)

Codeine + Butalbital + Acetaminophen + Caffeine
(Fioricet® with Codeine, generic)

Codeine + Butalbital + Aspirin + Caffeine
(*Fiorinal® with Codeine, generic*)

Codeine + Carisoprodol + Aspirin
(*generic*)

Dihydrocodeine + Acetaminophen + Caffeine
(*Trezix®, generic*)

Dihydrocodeine + Aspirin + Caffeine
(*Synalgos-DC*)

Hydrocodone + Acetaminophen
(*Hycet®, Lorcet®, Lorcet® HD, Lorcet® Plus, Lortab®, Lortab® Elixir, Norco®, Verdrocet®, Vicodin®, Vicodin® ES, Vicodin® HP, Xodol®, Zamicet®, generic*)

Hydrocodone + Ibuprofen
(*Ibudone®, Reprexain®, Vicoprofen®, Xylon®, generic*)

Oxycodone + Acetaminophen
(*Endocet®, Oxycet®, Percocet®, Primlev®, Roxicet®, Xartemis XR™, generic*)

Oxycodone + Aspirin
(*Percodan®, generic*)

Oxycodone+ Ibuprofen
(*generic*)

Tramadol + Acetaminophen
(*Ultracet®, generic*)

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Executive Summary

Introduction

The opioid analgesic agents have been used for centuries and are the most commonly used pharmacologic agents for the treatment of moderate to severe pain. Opioid analgesics stimulate opiate receptors and produce pain relief without producing loss of consciousness. The use of opioid-nonopioid combination medications was expected to offer advantages in adding nonopioid to either reduce anxiety (e.g. butalbital), reduce associated muscle spasm or spasticity (e.g. carisoprodol), or add independent analgesic activity affording an opioid sparing effect (e.g. acetaminophen, aspirin, ibuprofen). Although reducing opioid requirements might limit opioid adverse events and the development of tolerance or abuse, opioids have a wide therapeutic window while adjuvants are often associated with organ toxicity (e.g acetaminophen-hepatotoxicity, ibuprofen/aspirin-gastrointestinal toxicity) and a ceiling effect to their analgesic potency (e.g. ibuprofen 400 mg, acetaminophen 1 gm).

This report reviews the efficacy of 12 opioid combinations, including codeine, dihydrocodeine, hydrocodone, oxycodone and tramadol in various combinations with acetaminophen, aspirin, butalbital, caffeine or ibuprofen. All agents are scheduled according to the Controlled Substances Act, ranging from CII (oxycodone and hydrocodone containing products) to CV (codeine/acetaminophen preparations). The agents are labeled for use in mild to moderately severe pain; muscular headache; tension-type headache; acute, painful skeletal muscle conditions and acute pain. All agents are available as tablets or capsules for oral use. Three combinations are available in liquid dosage formulations and one agent, Xartemis XR™ (oxycodone/acetaminophen), is an oral tablet containing both immediate- and extended-release components.

The World Health Organization analgesic ladder addresses pain relief strategies at three levels. Non-opioid pain relievers are used at the lowest level, weak opioid agents (codeine) are used for moderate pain and strong opioid agents (morphine, hydromorphone, oxymorphone, methadone and fentanyl) are recommended for the highest level of pain. No guideline specifically supports the use of combination opioid products. When using acetaminophen/opioid combination products, patients should not take additional acetaminophen containing medications. Overall, the routine use of opioids for acute pain is not recommended. The use of codeine or barbiturates in headache pain is not recommended because the pain intensity is generally mild to moderate and the agents may cause medication-overuse headache.

Children should avoid aspirin- and codeine-containing medications. Patients who are known rapid metabolizers of codeine are at risk of toxicity, and slow metabolizers may not achieve pain relief. The selection of an opioid for pain relief should include consideration of the severity of pain, chronicity, type of pain, status of the patient as opioid-naïve or experienced, age, pregnancy status, renal and hepatic function, other diagnosis, concomitant medications, dosage formulation, abuse/misuse potential and a careful consideration of risk of harm vs. benefit.

Clinical Efficacy

Clinical experience with the combination opioid agents in the treatment of pain is limited to 2 systematic reviews/meta-analyses involving 22 clinical trials; a meta-analysis of 39 Cochrane reviews involving approximately 50,000 people; and 15 other randomized, controlled trials not included in any of the systematic reviews. Comparative evidence was not found for acetaminophen/butalbital/caffeine/codeine, carisoprodol/aspirin/codeine, dihydrocodeine/acetaminophen/caffeine, dihydrocodeine/aspirin/caffeine or aspirin/oxycodone or for Xartemis XR™. For outcome measures of pain control the evidence does not support the superiority of one combination opioid preparation over another. Stronger opioid combinations are likely more effective than weaker opioids for severe pain, while moderate opioids are often adequate for moderate pain. Opioid side effects were more common with stronger opioids and codeine containing combinations.

- Aspirin/butalbital/caffeine/codeine (ABCC) was more efficacious than acetaminophen/codeine for severe and overall pain, perhaps due to the additional antianxiety effects afforded by butalbital.
- No differences were observed for acetaminophen + tramadol (AT) versus acetaminophen/codeine or acetaminophen/hydrocodone in a variety of settings including dental surgery, outpatient surgery, ankle sprain and chronic pain. Limited evidence suggests that AT is less efficacious than stronger opioid combinations (e.g. oxycodone), while placebo controlled trials found AT was superior to acetaminophen/codeine and better tolerated.
- Ibuprofen + oxycodone (IO) was at least as efficacious as other opioid combinations, with a longer duration of analgesia and a higher risk of drowsiness.
- Doses of ibuprofen + hydrocodone (IH) within the FDA prescribing recommendations of 10 mg/dose resulted in efficacy similar to acetaminophen/oxycodone and acetaminophen/codeine. The acetaminophen component of the combination analgesic comparator was greater than the currently marketed 325 mg per tablet/capsule, which may have biased the findings. Additionally, the superiority of the higher dose hydrocodone regimen (ibuprofen 400 mg + hydrocodone 15 mg) likely reflects the higher than Food and Drug Administration (FDA)-approved daily dosage of hydrocodone 10 mg, that extends the duration of action due to pharmacokinetic and not true efficacy factors.
- Evidence does not support a difference in efficacy or safety for acetaminophen + oxycodone (AO) vs other comparators (acetaminophen/hydrocodone, acetaminophen/codeine, ibuprofen/hydrocodone).
- Overall, evidence does not support a difference in efficacy or safety for acetaminophen + hydrocodone (AH) vs other comparators (acetaminophen/hydrocodone or acetaminophen/tramadol).
- Acetaminophen + codeine (AC) was a comparator in 13 of the 18 evidence studies included in this report. Overall, evidence suggests that AC may be inferior to comparators, though not statistically significantly in any of the systematic reviews.

Safety

The most common adverse effects associated with the opioid analgesics include nausea,

vomiting, sedation, pruritus and constipation. Serious adverse effects frequently reported with opioid use include: respiratory depression, urinary retention, hypotension and delirium. Clinical trials demonstrate no differences in rates of serious adverse events. Weak evidence finds strong opioids and codeine-containing preparations are more commonly associated with adverse events.

Summary:

Overall, combination opioid analgesic agents are effective treatment options for acute pain disorders. Evidence showed no consistent differences between agents, although the single meta-analysis of 39 Cochrane Reviews showed oxycodone + ibuprofen was superior to other combination therapies. Evidence did not show substantial differences in adverse events among agents. Consideration should be given to the whether carisoprodol/aspirin/codeine should be given preferred status, as guidelines recommend avoiding the combination of opioid with skeletal muscle relaxants, and there is a lack of evidence to support their efficacy. Xartemis XR™ affords the benefit of extended pain relief, although guidelines do not recommend the use of long acting preparations for acute pain. Pain management must be individualized for each patient.

Introduction

The opioid analgesics are a class of agents that stimulate opiate receptors and produce pain relief without producing loss of consciousness.[1,2] These agents may be naturally occurring, semisynthetic, or synthetic. The opioid analgesics are divided into categories based on receptor subtype and potency. These agents are available in various combinations with non-steroidal anti-inflammatory agents (NSAIDs), aspirin, acetaminophen, butalbital or caffeine for labeled indications ranging from mild to moderately severe pain; muscular headache; tension-type headache; acute, painful skeletal muscle conditions and acute pain. This review will focus on the opioid combination products. Currently, twelve agents are approved for use in the United States: butalbital/acetaminophen/caffeine/codeine, butalbital/aspirin/caffeine/codeine, carisoprodol/aspirin/codeine, codeine/acetaminophen, dihydrocodeine/acetaminophen/caffeine, dihydrocodeine/aspirin/caffeine, hydrocodone/acetaminophen, hydrocodone/ibuprofen, oxycodone/acetaminophen, oxycodone/aspirin, oxycodone/ibuprofen, tramadol/acetaminophen. Oxycodone- and hydrocodone-containing preparations are Drug Enforcement Agency (DEA) schedule II (CII), dihydrocodeine-containing products are CIII, codeine products in combination with other central nervous system depressants (butalbital, carisoprodol) are CIII, tramadol-containing products are CIV and codeine with acetaminophen is designated CV. Each of the agents is available for oral use as tablets or capsules. Three combinations are available in liquid dosage formulations, codeine/acetaminophen, hydrocodone/acetaminophen and oxycodone/acetaminophen. Xartemis XR™ (oxycodone/acetaminophen) is an oral tablet containing both immediate- and extended-release components. *Dosage and Administration*

The selection of an opioid for pain relief should include consideration of the severity of pain, chronicity, type of pain, status of the patient as opioid-naïve or experienced, age, renal and hepatic function, other diagnoses, concomitant medications, dosage formulation, abuse/misuse potential and a careful consideration of risk of harm vs. benefit.[3-5] Short-term administration is recommended for carisoprodol/aspirin/codeine, hydrocodone/ibuprofen, oxycodone/ibuprofen and tramadol/acetaminophen, although studies are unavailable to validate use of any opioid combination preparation for long-term use in noncancer pain.[6,7] See *Table 1* for a summary of agents.

Table 1: Product Comparison

Product	DEA Class	Available Oral Formulations	Indication/Uses	Oral Dose Range, Adults	Oral Dose Range, Pediatrics	Generic
Codeine + Acetaminophen	**CV**	**Generic** Elixir: 120 mg-12 mg/5 ML Solution: 120 mg-12 mg/5 ML Tablet: 300 mg-15 mg 300 mg-30 mg 300 mg-60 mg **Capital w/Codeine** Suspension: 120 mg-12 mg/5 ML **Tylenol with Codeine No. 3** Tablet: 300 mg-30 mg **Tylenol with Codeine No. 4** Tablet: 300 mg-60 mg	Pain, Mild to moderately severe	**Pain, Mild to Moderately Severe** • Tablets: Codeine 15-60 mg (ACTM 300-1000 mg) every 4 hours as needed. • Suspension/Solution: 15 mL every 4 hour as needed • Extended use is not recommended • MAX: ACTM 4000 mg daily	Pain, Mild to Moderately Severe Age 3-6 years Suspension: 5 mL 3-4 times daily Age 7-12 years Suspension/Solution: 10 mL 3-4 times daily Age > 12 years Suspension/Solution: 15 mL 4 times daily as needed **MAX: ACTM 4000 mg daily**	Yes
Codeine + Butalbital + ACTM + Caffeine	**CIII**	**Generic** Capsule: 300 mg-50 mg-40 mg-30 mg 325 mg-50 mg-40 mg-30 mg **Fioricet with Codeine** Capsule: 300 mg-50 mg-40 mg-30 mg	Muscular headache Tension-type headache	**Muscular and Tension-type Headache** • 1-2 caps every 4 hours • MAX: 6 caps daily **Extended/Repeated use may lead to physical dependence	Not established	Yes
Codeine + Butalbital + Aspirin + Caffeine	**CIII**	**Generic** Capsule: 325 mg-50 mg-40 mg-30 mg	Relief of complex tension headache symptoms	**Relief of complex tension headache symptoms** • 1-2 caps every 4 hours as needed • MAX: 6 caps daily **Extended/Repeated use may lead to physical dependence	Not established	Yes

Product	DEA Class	Available Oral Formulations	Indication/Uses	Oral Dose Range, Adults	Oral Dose Range, Pediatrics	Generic
Codeine + Carisoprodol + Aspirin	**CIII**	**Generic** Tablet: 325 mg-200 mg-16 mg	Relief of discomfort associated with acute, painful, skeletal muscle conditions in adults	**Relief of Discomfort Associated with Acute, Painful, Skeletal Muscle Conditions in Adults** • 1-2 tabs 4 times daily • MAX: 8 tabs daily • MAX Duration: 2-3 weeks	Not established	Yes
Dihydrocodeine + Acetaminophen + Caffeine	**CIII**	**Generic** Capsule: 320.5 mg-30 mg-16mg **Trezix** Capsule: 320.5 mg-30 mg-16mg	Pain, Moderate to moderately severe pain	**Pain, Moderate to Moderately Severe Pain** • 2 caps every 4 hour as needed; titrate to pain relief MAX: 10 capsules per 24 hours	Not established	
Dihydrocodeine + Aspirin + Caffeine	**CIII**	**Generic** Capsule: 356.4 mg-30 mg-16 mg **Synalgos-DC** Capsule: 356.4 mg-30 mg-16 mg	Pain, Moderate to severe	**Pain, Moderate to Severe** • 2 caps every 4 hours as needed	Not established in age ≤ 12 years No dosage recommendation for adolescents	Yes
Hydrocodone + Acetaminophen	**CII**	**Generic** Elixir: 325 mg-7.5 mg/15 ML Solution: 108 mg-2.5 mg/5 ML 325 mg-7.5 mg/15 ML 325 mg-10 mg/15 ML 217 mg-5 mg/10 ML 163 mg-5 mg/7.5 ML 167 mg-2.5 mg/5 ML Tablet: 300 mg-5 mg 300 mg-7.5 mg 300 mg-10 mg 325 mg-2.5 mg 325 mg-5 mg 325 mg-7.5 mg	Pain, Moderate to moderately-severe	**Pain, Moderate to Moderately-Severe** Tablets: • 5-325 mg: 1-2 tabs every 4-6 hours as needed. MAX 12 tabs daily • 7.5-325 mg or 10-325 mg: 1 tab every 4-6 hours as needed. MAX 6 tabs daily • 5-300 mg: 1-2 tabs every 4-6 hours as needed. MAX 8 tabs daily • 7.5-300 mg or 10-300 mg: 1 tab every 4-6 hours as needed. MAX 6 tabs daily	Pain, Moderate to Moderately-Severe Age ≥ 2 years Solution 7.5-325 mg/15 mL: 0.27 mL/kg every 4-6 hours as needed. MAX 6 doses daily. Solution 10 mg-300 mg/15 mL: 0.2 mL/kg every 4-6 hours as needed. MAX 6 doses daily. Solution 10-325 mg/15 mL: 0.2 mL/kg every 4-6 hours as needed. MAX 6 doses daily.	Yes

Product	DEA Class	Available Oral Formulations	Indication/Uses	Oral Dose Range, Adults	Oral Dose Range, Pediatrics	Generic
		325 mg-10 mg **Hycet** Elixir: 325 mg-7.5 mg/15 ML **Lorcet HD** Tablet: 325 mg-10 mg **Lorcet** Tablet: 325 mg-5 mg **Lorcet Plus** Tablet: 325 mg-7.5 mg **Norco** Tablet: 325 mg-5 mg 325 mg-7.5 mg 325 mg-10 mg **Verdrocet** Tablet: 325 mg-2.5 mg **Vicodin ES** Tablet: 300 mg-7.5 mg **Vicodin HP** Tablet: 300 mg-10 mg **Vicodin** Tablet: 300 mg-5 mg **Xodol** Tablet: 300 mg-5 mg 300 mg-7.5 mg 300 mg-10 mg 325 mg-10 mg **Zamicet** Solution:		Oral Solution: • 7.5-325 mg/15 mL: 15 mL every 4-6 hr as needed. MAX 90 mL daily • 10-300 mg/15 mL: 11.25 mL every 4-6 hr as needed. MAX 67.5 mL daily • 10-325 mg/15 mL: 15 mL every 4-6 hours as needed. MAX: 90 mL daily • MAX ACTM Dose: 4gm/day	• Weight-based dosing is preferred (tables are available online) • Children ≥ 50 kg use adult dosing	

Product	DEA Class	Available Oral Formulations	Indication/Uses	Oral Dose Range, Adults	Oral Dose Range, Pediatrics	Generic
		325 mg-10 mg/15 ML				
Hydrocodone + Ibuprofen	**CII**	**Generic** Tablets: 5 mg-200 mg 7.5 mg-200 mg 10 mg-200 mg **Ibudone** Tablets: 5 mg-200 mg 10 mg-200 mg **Reprexain** Tablets: 2.5 mg-200 mg 5 mg-200 mg 10 mg-200 mg **Vicoprofen** Tablets: 7.5 mg-200 mg **Xylon 10** Tablets: 10 mg-200 mg	Pain, acute **Non-labeled** Pain, chronic	**Pain, Acute** • 2.5-10 mg hydrocodone & IBU 200 mg every 4-6 hours as needed. • MAX 5 tablets in 24 hours for less than 10 days.	Not Established in children < 16 years of age Age ≥ 16 years: • 2.5-10 mg hydrocodone & IBU every 4-6 hours as needed. MAX 5 tablets in 24 hours for less than 10 days.	Yes
Oxycodone + Acetaminophen	**CII**	**Generic** Solution: 325 mg -5 mg/5 ML Tablet: 325 mg-2.5 mg 325 mg-5 mg 325 mg-7.5 mg 325 mg-10 mg **Endocet** Tablet: 325 mg-2.5 mg	Pain, Moderate to moderate-severe	**Pain, Moderate to Moderately Severe** Immediate-release: • Oxycodone 2.5 mg-10 mg & ACTM 325 mg-650 mg every 6 hours as needed. • MAX: oxycodone 60 mg daily • MAX: ACTM 4 gm daily Extended-release: • 15 mg & ACTM 650 mg every 12 hr; may give 2nd dose at 8 hrs with subsequent doses at 12-hr	Not established *~*~*~*~*~* **Off-label recommendation** (American Pain Society) Moderate pain: Oxycodone 0.1-0.2 mg/kg/dose every 4-6 hr as needed. MAX initial dose 5 mg oxycodone Severe pain: Oxycodone 0.2 mg/kg/dose every 4-6 hr as	Yes

Product	DEA Class	Available Oral Formulations	Indication/Uses	Oral Dose Range, Adults	Oral Dose Range, Pediatrics	Generic
		325 mg-5 mg 325 mg-7.5 mg 325 mg-10 mg **Percocet** Tablet: 325 mg-2.5 mg 325 mg-5 mg 325 mg-7.5 mg 325 mg-10 mg **Primlev** Tablet: 300 mg-5 mg 300 mg-7.5 mg 300 mg-10 mg **Roxicet** Solution: 325 mg-5 mg/5 ML Tablet: 325 mg-5 mg **Xartemis XR** Tablet, Extended Release: 325 mg-7.5 mg		intervals. • Xartemis XR™ is not interchangeable with other products due to pharmacokinetic differences. • Do not stop abruptly in physically dependent patients • MAX: ACTM 4 gm daily	needed. MAX initial dose 10 mg. MAX ACTM: Age < 45 kg: 90 mg/kg/day MAX ACTM: Age ≥ 45 kg: 4 gm daily •	
Oxycodone + Aspirin	**CII**	**Generic** Tablet: 325 mg-4.8355 mg **Percodan** Tablet: 325 mg-4.8355 mg	Pain, Moderate to severe	**<u>Pain, Moderate to Severe</u>** • 1 tab every 6 hours as needed for pain. MAX: 12 tabs per 24 hours	Not established *~*~*~*~*~*~*~ **Off-label recommendation** (American Pain Society) Oxycodone 0.1-0.2 mg/kg/dose (max dose 5 mg/dose) every 4-6 hours as needed MAX: Aspirin 4 gm/day	Yes
Oxycodone + Ibuprofen	**CII**	**Generic** Tablet:	Pain, Acute to moderate Short-term (≤ 7 days)	**<u>Pain, Acute to Moderate</u>** • 1 tablet every 6 hours as needed.	Not established	Yes

Product	DEA Class	Available Oral Formulations	Indication/Uses	Oral Dose Range, Adults	Oral Dose Range, Pediatrics	Generic
		400 mg-5 mg		• MAX: 4 tablets per 24 hours • MAX Duration: 7 days	Adolescents ≥ 14 years; Use adult dosing	
Tramadol + Acetaminophen	**CIV**	**Generic** Tablet: 325 mg-37.5 mg **Ultracet** Tablet: 325 mg-37.5 mg	Acute Pain ***Non-labeled Use*** Diabetic Peripheral Neuropathy	**Acute Pain**: • Two tabs every 4-6 hours as needed • Duration: Five days or less • MAX: 8 tabs a day	Not Established	Yes

Key: ACTM=acetaminophen; IBU=ibuprofen

Disease Overview - Pain

The most commonly quoted definition for pain comes from the International Association for the Study of Pain, which defined pain as "an unpleasant sensory or emotional experience associated with actual or potential tissue damage or described in terms of such damage."[8] Pain is indicative of physical harm or a disease process. Acute, or nociceptive, pain is "the normal, predicted physiologic response to an adverse chemical, thermal, or mechanical stimulus associated with surgery, trauma, or acute illness."[9] Nociceptors are found below the skin, tendons, joints and body organs and detect cutaneous, somatic and visceral pain.[10-12] Pain is the rapid warning relay from the central nervous system (CNS) to the motor neurons as a result of detected physical harm. Pain is the most common reason people enter the health care system and patients with pain have higher rates of health care resource utilization, disability and poorer overall health status than those without pain.[13, 14]

The most commonly reported sites of acute pain are severe headache/migraine (16.1%), low back pain (28.1%), neck pain (15.1%), knee pain (19.5%), shoulder pain (9.0%), finger pain (7.6%) and hip pain (7.1%).[15] Additionally, acute pain associated with inpatient surgical procedures affects 46 million Americans yearly.[16] Patients visiting emergency departments frequently cite pain as the primary complaint with 45% reporting the severity as moderate to severe.[17] Acute pain is typically self-limiting with healing occurring over days to weeks although pain may persist more than 3 months as healing occurs. Acute pain often presents with hypertension, tachycardia and diaphoresis due to autonomic nervous activation. Inadequate pain control can result in impaired sleep, depression, mood, debilitation, deconditioning and disability, hypercoagulability, impaired immunity and chronic pain.[16,18,19].

In general, opioids and non-steroidal anti-inflammatory drugs (NSAIDs) are very effective in the treatment of acute pain.[7] Treatment with nonopioid analgesics (e.g. NSAIDs, acetaminophen, aspirin, other adjuvants) combined with nonpharmacologic therapy is considered appropriate first-line therapies for moderate pain. In the setting of headache, the risk of opioid-induced medication overuse headache and opioid adverse events may be greater than any benefit achieved.[20] When opioids are used, they should be used in combination with nonpharmacologic therapy and nonopioid analgesic therapy.[7] The use of nonpharmacologic and nonopioid therapy for acute pain has been associated with less harm.[7] Opioids are usually second-line options for treatment of acute pain due to small to moderate short-term benefits and potential for serious harms, including opioid use disorder, overdose and motor vehicle injury.[7] The 2015 Substance Abuse and Mental Health Services Administration's (SAMHSA) National Survey on Drug Use and Health (NSDUH) found more than 2 million people initiated opioid use in 2015. Over 12 million people reported opioid misuse and 2 million qualified as having an opioid use disorder.[21]

Supporting opioids as second-line therapy, even in severe pain, is the Oxford League.[22] This group reviewed a large number of systematic reviews of patients with moderate to severe acute pain for the outcome of 50% reduction in pain over 4 to 6 hours compared to placebo in double-blind, single-dose studies. In order of greatest to lowest response, they found ibuprofen 800 mg efficacious in 100% of patients. Effective at a lower rate were oxycodone 10 mg +

acetaminophen 1000 mg (67%) > oxycodone 10 mg + acetaminophen 650 mg (66%) > oxycodone 5 mg + acetaminophen 500 mg (60%) > acetaminophen 1000 mg + codeine 60 mg (57%) > oxycodone 5 mg + acetaminophen 1000 mg (55%).[22]

The World Health Organization (WHO) recommendations include an analgesic ladder addressing cancer pain relief strategies at three levels and often extrapolated for acute pain.[23] Nonopioid pain relievers are used at the lowest level, weak opioid agents (codeine, tramadol) are used for moderate pain and strong opioid agents (morphine, hydromorphone, oxymorphone, methadone and fentanyl) are recommended for the highest level of pain. Considerations for pain management include, characterization of the pain complaint (PQRST; precipitating, quality, relief/radiation, severity, temporal relationship), opioid risk assessment (ABCDPQRS; alcohol use, benzodiazepine use; clearance/metabolism of the drug; delirium/dementia/fall risk, psychiatric comorbidities, query the primary medical practitioner, respiratory insufficiency/sleep apnea, safe driving, work, storage and disposal),[24] evaluation of comorbidities, personal and family substance abuse history, age, individual differences, previous opioid experiences and current exposure, drug-specific differences, use of the least invasive route of administration and consideration of adherence. Doses are increased until analgesia is obtained or dose-limiting side effects occur. Consideration is given to around the clock vs as-needed dosing. Monitoring includes analgesic efficacy, side-effects, aberrant behaviors, therapy modifications over time with follow-up based on the patient's clinical and social circumstances.[25]

In the treatment of acute pain, stronger analgesia should be administered for a limited time and stepped down to less potent opioid and non-opioid analgesia.[25-42] Some guidelines recommend prescribing opioids in multiples of 7-days supply to reduce the incidence of supply ending on a weekend.[27]

Clinical Practice Guideline Recommendations for Use of Opioid Analgesics

There are many guidelines relating to the appropriate use of opioid therapy.[24] No guideline specifically supports the use of combination opioid products. Those that suggest the use of opioids with adjuvant therapy, or in combination with conventional therapy, do not define the additional therapy. All guidelines suggest starting therapy with nonpharmacologic or over-the-counter (OTC) treatment with NSAID, COX-2 inhibitors or acetaminophen for mild to moderate pain. Treatment of moderate to severe pain may not be superior with opioid therapy compared to nonopioids. Overall, the routine use of opioids for acute pain is not recommended.

Most guidelines recommend:

- Considering the risk-benefit tradeoff for opioids vs nonopioid therapy
- Opioid risk mitigation strategies (e.g. screening for preexisting risk factors for developing opioid misuse or abuse potential
- Prior drug or alcohol abuse
- Psychological evaluation for patients at risk of abuse or misuse
- Use of treatment agreements with clearly defined expectations
- Urine drug screening

- Regular screening for pain relief, side effects, and quality of life
- Ongoing evaluation of lowest effective dosages
- Recommend the selection of opioid therapy based on efficacy, tolerability and patient related variables (e.g. elderly, neuropathic pain, convenience, renal function, constipation)
- Consider drug-interactions particularly important when using tramadol (with regard to seizures and serotonin syndrome)
- Do not recommend long-acting agents for opioid naïve patients or in the treatment of acute or noncancer pain; and recommend treatment discontinuation if meaningful improvement is not seen in pain or function.

Table 2 summarizes published guidelines with specific recommendations concerning the use of opioids.

Table 2: Clinical Practice Guideline Recommendations for Use of Opioid Analgesics*

*Please see the full guideline for complete recommendations

CDC Guideline for Prescribing Opioids for Chronic Pain – United States, 2016[7]
No recommendation directly addresses combination opioid medications Applicable to chronic pain management OUTSIDE of active cancer treatment, palliative care and end-of-life care • Nonpharmacologic/nonopioid therapies are preferred for chronic pain. Use opioids only if anticipated benefit in pain and function outweigh risks. Opioids should be combined with nonpharmacologic therapy (as appropriate) • Discontinue therapy no clinically meaningful improvement in pain/function outweighing patient risks. • Initiate chronic pain therapy with immediate-release opioids at the lowest dosage. Morphine doses about 50 morphine milligram equivalent (MME) require careful assessment of individual risks and benefits. Doses above 90 MME require careful justification. • When used for acute pain, use the lowest effective dose of immediate-release opiates for the expected duration of pain (≤3 days is often adequate, >7 days is rarely needed). • Evaluate benefits/harms at 1-4 weeks and at least every 3 months. Taper and discontinue opioid if benefits do not continue to outweigh harms. • Evaluate periodically for risk factors, offering naloxone for overdose risk, abuse disorder, dosages ≥50 morphine MME/day or concurrent benzodiazepine. • Review controlled prescription history on state prescription drug monitoring program (PDMP) at the start of therapy and periodically from every prescription to every 3 months. • Annual urine drug testing for chronic pain treatment to assess prescribed, controlled and illicit drugs. • Avoid prescribing opioid pain medications and benzodiazepines whenever possible. • Use evidence-based treatment in patients with opioid use disorders (e.g. buprenorphine or methadone with behavioral therapies).
American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis(OA) of the hand, hip, and knee.[36]
No recommendation directly addresses combination opioid medications **Pharmacologic Strategies for Hand OA** <u>Conditionally recommended</u>: Topical or oral NSAIDs (including trolamine salicylate and COX-2 selective inhibitors), topical capsaicin or tramadol • Conditionally recommend persons ≥ 75 year of age use topical vs oral NSAIDs <u>Conditional recommendation against</u>: Intraarticular therapies, opioid analgesics

Patients requesting trapeziometacarpal (TMC) joint intraarticular injection:

- Use corticosteroids or hyaluronates. For erosive/inflammatory interphalangeal OA use oral methotrexate (MTX) or sulfasalazine.

Pharmacologic Strategies for Knee OA

Conditionally recommended: Acetaminophen, oral NSAIDs, tramadol, intraarticular corticosteroid injections

- Patients on low-dose aspirin: Use nonselective oral NSAID other than ibuprofen plus a proton-pump inhibitor (PPI)

Conditional recommendation against: chondroitin sulfate, glucosamine, topical capsaicin

No recommendation: Intraarticular hyaluronates, duloxetine, opioid analgesics

Patients failing non-pharmacologic and pharmacologic therapies and unable/unwilling to undergo total joint arthroplasty:

- Recommended: Opioid analgesics
- Conditionally recommended: Duloxetine

Pharmacologic Strategies for Hip OA

Conditionally recommended: Acetaminophen, oral NSAIDs, tramadol, intraarticular corticosteroid injections

Conditional recommendation against: Chondroitin sulfate, glucosamine

No recommendation: Topical NSAIDs, intraarticular hyaluronate injections, duloxetine, opioid analgesics

Patients failing non-pharmacologic and pharmacologic therapies and unable/unwilling to undergo total joint arthroplasty:

- Recommended: Opioid analgesics

Acute pain assessment and opioid prescribing protocol. Health care protocol, 2014[24]

No recommendation directly addresses combination opioid medications

Non-inclusive list of pain conditions for which opioids are almost never indicated: fibromyalgia, headache, self-limited illness (e.g. sore throat), uncomplicated neck/back/musculoskeletal pain

Non-traumatic tooth pain

- Do not prescribe opioids without examination and diagnosis of the underlying reason for tooth pain (e.g. tests and x-rays)

Assess the benefit of opioid therapy vs opioid risks (shared decision making)

- High risk of adverse event: other analgesics, NSAIDs, physical or psychological interventions or other non-opioid therapies

Prescribing Opioids (shared decision making)

- Prescribe ≤3 days (2 pills), low-dose, short-acting opioid
- Tramadol is an atypical opioid to be considered individually
- Never prescribe long-acting/extended release products
- Caution in the elderly
- Schedule followup appointment with PCP within 3-5 days
- Review side effects
- Review safe driving, work, storage and disposal
- Maximize appropriate non-opioid therapies

American Academy of Orthopaedic Surgeons appropriate use criteria for non-arthroplasty treatment of osteoarthritis of the knee. (2013)[37]

- Prescription of narcotic medicine for refractory pain (oral or transcutaneous opioids) should be monitored, intermittent or low dose **in conjunction with other therapies** (other therapies not defined)

The treatment of restless legs syndrome (RLS) and periodic limb movement disorder in adults—an update for 2012: practice parameters with an evidence-based systematic review and meta-analyses[38]

No recommendation directly addresses combination opioid medications

Clinicians can treat RLS patients with opioids

Values and Trade-Offs of Opioid Therapy:

- Opioid data shows clinical effectiveness in treating RLS with a low level of evidence.
- Side effects can include an undefined potential for abuse in predisposed patients and a possible risk for the development or worsening of sleep apnea. Therefore, patients should be clinically monitored for the development of symptoms.
- In general, however, this medication is very well tolerated and has a lower risk of augmentation than is seen in the dopaminergic medications.

VA/DoD clinical practice guideline for the non-surgical management of hip and knee osteoarthritis (OA) (2014)[39]

- Persistent, moderate or moderately severe OA pain may be treated with duloxetine or tramadol as an alternative **or adjunct to oral NSAIDs** (Level B recommendation)
- Persistent, severe OA pain with contraindications, inadequate response or intolerance to non-opioid therapies and tramadol, clinicians may consider non-tramadol opioids (Level C recommendation).
- Strong opioids should be considered as an option for pain relief for patients with chronic low back pain or osteoarthritis, and only continued if there is ongoing pain relief. Regular review of treatment is required (Level B recommendation)
- Specialist referral or advice should be considered if there are concerns about rapid-dose escalation with continued unacceptable pain relief, or if >180 mg/day morphine equivalent dose is required (Level D recommendation)

Pain management in older adults. In: Evidence-based geriatric nursing protocols for best practice (Revised 2012)[28]

No recommendation directly addresses combination opioid medications

- Administer pain drugs on a regular basis to maintain therapeutic levels. Use as needed (PRN) medications for breakthrough pain
- Acetaminophen is preferred nonopioid for mild-to-moderate pain.
- Use opioids for moderate-to-severe pain and nonopioids for mild-to-moderate pain.

Low Back Disorders (2011)[29]

Acute Low Back Pain

- Recommend limited use of opioids for severe acute low back pain without radicular pain.
- Routine use of opioids NOT recommended

Subacute Low Back Pain

- Routine use of opioids NOT recommended

Chronic Low Back Pain

- A trial of opioid therapy for chronic severe back or leg pain may be required
- Routine use of opioids NOT recommended

Radicular Pain Syndromes (including sciatica), Spinal Stenosis, Spinal Fractures, Sacroiliitis, Spondylolisthesis, Facet Degenerative Joint Disease

- Opioids NOT recommended

Post-Operative Low Back Pain

- Limited use of **opioids as adjunctive therapy** to more effective treatments (not specified)

NICE guidelines [CG173] Neuropathic pain in adults: pharmacological management in non-specialist settings (published 2013, updated December 2014)[30]

No recommendation directly addresses combination opioid medications

- Neuropathic pain (except trigeminal neuralgia) should initially be treated with amitriptyline or duloxetine or gabapentin or pregabalin
- If the initial treatment is not effective or is not tolerated, offer one of the remaining 3 drugs, and consider switching again if the second and third drugs tried are also not effective or not tolerated
- Tramadol should be used only for short-term acute rescue therapy

Shoulder Disorders (2011)[31]

No recommendation directly addresses combination opioid medications

Acute, Subacute, Chronic Shoulder Pain

- Judicious use of opioids for acute severe shoulder pain
- Opioids for select patients with subacute or chronic shoulder pain
- Routine use of opioids NOT recommended

Post-Operative Pain, Superior Labral Anterior Posterior (SLAP) and Other Labral Tears, Acromioclavicular Sprains or Dislocations, Shoulder (Glenohumeral and Acomioclavicular Joint) Osteoarthritis, Adhesive Capsulitis

- Judicious use of opioids

Rotator Cuff Tendinopathies, Bicipital Tendon Tears, Pectoral Strains and Tears, Proximal Humeral Fractures, Clavicular Fractures, Osteonecrosis, Brachial Plexus Injuries

- No opioid recommendations

Shoulder Dislocation and Instability

- Judicious use of short-term use opioids for select patients with acute moderate to severe pain or post-operative pain
- Opioids are NOT recommended for pain management of subacute or chronic pain associated with shoulder dislocation

Trigger Points/Myofascial Pain

- Opioids are NOT recommended for muscle tenderness (myalgias) or myofascial pain

American Society of Interventional Pain Physicians (ASIPP) guidelines for responsible opioid prescribing in chronic non-cancer pain: Part I--evidence assessment (2012)[34]

No recommendation directly addresses combination opioid medications

- The short-term effectiveness of opioids is fair, whereas the long-term effectiveness of opioids is limited due to a lack of long-term (> 3 months) high quality studies, with fair evidence with no significant difference between long-acting and short-acting opioids.
- Among the individual drugs, most opioids have fair evidence for short-term and limited evidence for long-term due to a lack of quality studies.
- The evidence for the effectiveness and safety of chronic opioid therapy in the elderly for chronic non-cancer pain is fair for short-term and limited for long-term due to lack of high quality studies; limited in children and adolescents and patients with comorbid psychological disorders due to lack of quality studies; and the evidence is poor in pregnant women.

American Society of Interventional Pain Physicians (ASIPP) guidelines for responsible prescribing in chronic non- cancer pain: part 2 – guidance[33]

No recommendation directly addresses combination opioid medications

- There is no difference in efficacy or adverse effects with short- or long-acting opioids

Clinical policy: critical issues in the prescribing of opioids for adult patients in the emergency department (ED) (2012)[35]

No recommendation directly addresses combination opioid medications

Are short-acting opioids more effective than other medications for treatment of acute low back pain? (all level C evidence)

- First-line consider nonopioid analgesics, nonpharmacologic therapies
- Reserve opioids for more severe pain or pain refractory to other analgesics
- Prescribe opioids at the lowest practical dose for limited duration (e.g. < 1 week) with consideration of risk of abuse, misuse or diversion.

Are short-acting CII more effective than CIII medications?

- For short-term relief of acute musculoskeletal pain short-acting opioids (e.g. hydrocodone, oxycodone) are appropriate with consideration of benefits and risks to the individual patient (Level B evidence)
- Evidence is insufficient to evaluate CII vs CIII medications for pain relief (Level C evidence)

For an exacerbation of noncancer chronic pain, do the benefits of opioids outweigh the potential harms? (all level C evidence)

- ED physicians should avoid routine prescribing of outpatient opioids
- If prescribed, use the lowest practical dose for limited duration (e.g < 1 week) with consideration of risk of abuse, misuse or diversion.
- If practical, honor existing patient-physician pain contracts/treatment guidelines, consider past prescribing patterns and information from prescription drug monitoring programs

Guideline for prescribing opioids to treat pain in injured workers (2013)[27]

Drug and Drug Combinations to Avoid

- Long-acting or extended release opioids for acute pain or post-operative pain in an opioid-naïve worker

Use is not recommended

- Carisoprodol
- **Any combination of opioids with benzodiazepines, sedative-hypnotics or barbituates**.
    - There may be specific indications for such combinations, such as the co-existence of spasticity. In such cases, a pain specialist consultation is strongly recommended. Consider alternatives such as tricyclic antidepressants or antihistamines to manage insomnia

Use with caution

- **OTC acetaminophen *with* acetaminophen combination opioids**
- Tramadol in patients at risk of seizures or who take other medications which can cause seizures (e.g. bupropion, serotonin reuptake inhibitors, tricyclic antidepressants)

Opioids in the acute phase (0-6 weeks after injury or surgery)

- Reserve opioids for post-surgery, severe pain (e.g. pain score ≥7), or when NSAIDs or nonpharmacologic therapies fail.
    - Evidence does NOT support opioids for the initial treatment of back sprains. IF prescribed, limit administration to ≤14 days.
- If pain does not improve to level 4 or less or function does not improve by ≥30% during the acute phase, continued opioid therapy is not warranted.
- Anticipate tapering the opioids off by 6 weeks.

Opioids in the subacute phase (6-12 weeks after injury or surgery)

- Screen the worker for comorbid conditions that may impact the response to opioid therapy (e.g. depression, PTSD)
- Re-examine and consider discontinuation or taper of concurrent sedative-hypnotics and/or benzodiazepines.

• Discontinue opioids if there is no clinically meaningful improvement in function compared to the acute phase, a severe adverse outcome occurred, worker has a non-nicotine substance abuse disorder or opioid use disorder
Managing chronic non-terminal pain in adults including prescribing controlled substances (2011)[40]
Manage expectations Initiate therapy with non-pharmacologic therapies followed by NSAIDs ± acetaminophen for chronic musculoskeletal or arthritis pain. • Caution NSAID/COX-2 inhibitor use in the elderly (GI/renal toxicity, hypertension, heart failure) Scheduled, long-acting opioids are preferred for continuous treatment. **Avoid long-term, daily treatment with short-acting opioids and opioid-combinations** For PRN dosing, prescribe small amounts expecting monthly (not daily) use.
Canadian guideline for safe and effective use of opioids for chronic noncancer pain: Clinical summary for family physicians. Part 1: General population (2011)[41]
No recommendation directly addresses combination opioid medications **Mild to Moderate Pain** • First line: Codeine or Tramadol • Second line: Morphine, oxycodone or hydromorphone **Severe Pain** • First line: Morphine, oxycodone or hydromorphone • Second line: Fentanyl • Third line: Methadone
Evidence-based guideline: treatment of painful diabetic neuropathy. Report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation (2011)[42]
No recommendation directly addresses combination opioid medications Class II evidence supports morphine, tramadol and oxycodone controlled release in lessening the pain of peripheral diabetic neuropathy. Treatment results in a moderate size effect, reducing pain 27% compared with placebo • Adverse effects: tramadol 18% sedation, nausea 23%, constipation 21%

Key: COX-2=cyclooxygenase-2 inhibitor drugs; PCP=primary care provider; Level B=Recommendations for patient management that may identify a particular strategy or range of management strategies that reflect moderate clinical certainty; Level C=Other strategies for patient management that are based on Class III studies, or in the absence of any published literature, based on panel consensus;

Disease Overview – Tension-type headache

Tension-type headache (TTH) varies in frequency from episodic (< 1 day/month) to chronic (≥15 days/month).[43,44] Episodic TTH is the result of peripheral mechanisms while chronic TTH is associated with central pain mechanisms. Episodic TTH is treated symptomatically and chronic TTH with prophylactic treatment. The prevalence of TTH is 78% of the US population, although most patients report episodic disease. Only 2-3% have chronic TTH through their lifetime. Women report TTH slightly more than men (5:4 ratio). The age of onset is between 25-30 years with a peak prevalence at 30-39 years of age. Risk factors include

poor self-rated health, difficulty relaxing after work and reduced hours of sleep. The number of days of work missed was three times higher for TTH than from migraine.[43-45]

TTH presents with bilateral, pain described as pressing or tightening, and of mild to moderate intensity either episodically or chronically. [43-45] Patients may have either photophobia or phonophobia and may have mild nausea. The diagnosis is based on a normal neurological examination and the patient's symptoms. A headache diary is helpful in differentiating between mild migraine and TTH. More intensive investigations are required if secondary headache is suspected, if the pattern of headache changes or in the presence of persistent neurologic or psychopathological abnormalities. Comorbidities should be treated and patient education to increase compliance with prophylactic therapy as TTH is seldom cured.[43,44,45]

Nonpharmacologic treatment measures include electromyography (EMG) biofeedback or cognitive behavior therapy (CBT), relaxation training, physical therapy and acupuncture. TTH is most commonly treated with over the counter analgesics (aspirin, acetaminophen or NSAIDs). Treatment response is inversely correlated with frequency of headaches. Chronic TTH places the patient at risk of medication overuse, as the associated symptoms of stress, anxiety and depression do not respond to analgesic therapy. Comorbidities should be treated, as indicated. Effective prophylactic therapies for chronic TTH include amitriptyline (first-line), mirtazapine, venlafaxine (second-line), clomipramine, maprotiline or mianserin (third-line).[43,45,46]

Clinical Practice Guidelines for Treatment of Tension-Type Headache

Clinical practice guidelines for treatment of tension-type headache are available from the National Institute for Health and Care Excellence (NICE)[47]; a multidisciplinary group of Canadian family physicians and specialists [48]; recommendations from otolaryngologic physicians on evidence-based treatments and expert opinion[49]; and the European Federation of Neurological Societies (EFNS) task force guidelines based on evidence and expert consensus.[43]

Overall, acute treatment recommendations include NSAIDs, acetaminophen or aspirin alone or in combination with caffeine. The use of codeine and barbiturates are not recommended due to the risk of medication-overuse headache. Opioids are not recommended because the pain of TTH is generally mild to moderate. No guideline clearly identified prophylactic therapy. UpToDate supports prophylactic pharmacotherapy with tricyclic antidepressants (e.g amitriptyline), other antidepressants (e.g. mirtazapine, venlafaxine), anticonvulsants (e.g. gabapentin, topiramate), tizanidine as well as trigger point injections with lidocaine or botulinum toxin injections.[50] *Table 3* presents the clinical practice guidelines for the treatment of tension/muscular headache.

Table 3: Clinical Practice Guidelines for the Treatment of Tension/Muscular Headache*
*Please see the full guideline for complete recommendations

Headaches in over 12s: Diagnosis and Management[47]
Opioids were not subdivided to codeine vs strong opioids
Tension type headache, acute treatment

• Consider aspirin, acetaminophen or NSAID considering patient preference, comorbidities and adverse event risk • **Do not offer opioids** for the acute treatment of tension-type headache
Guideline for primary care management of headache in adults[48]
Tension-type headache, acute • Consider ibuprofen, aspirin, naproxen, acetaminophen
Medical management of adult headache[49]
Tension-type headache, acute treatment • Consider acetaminophen, aspirin or NSAIDs alone or in combination with caffeine • **Avoid opioids**
EFNS guideline on the treatment of tension-type headache - report of an EFNS task force[43]
Acute treatment • Strongest recommendation: ibuprofen, ketoprofen, aspirin, naproxen, diclofenac, acetaminophen • Less well supported: caffeine combination products ○ Combinations of simple analgesics with codeine or barbiturates should not be used due to the risk of developing medication-overuse headache • **Opioid use increases the risk of medication-overuse headache and are not recommended**

Key: NSAID=nonsteroidal anti-inflammatory drug

Pharmacology

Opioid analgesics bind to receptors within and without the central nervous system (CNS).[1,2] Opioid analgesia is mediated by mu-, delta-, and kappa-opioid receptors. Activation of the mu-opioid receptor produces analgesic and euphoric effects associated with opioid use. Mu-opioid receptors are located within the CNS, gastrointestinal (GI) tract and peripherally in association with sensory nerves and mast cells.[1,2] Activation of opioid receptors results in differing responses between patients. Renal and hepatic function, age and genetic factors also affect an individual's response to opioids.[51,52]

Opioids are classified as full agonists, partial agonists or mixed agonist-antagonists.[1,2,53] Full mu-opioid receptor agonists produce analgesia without a ceiling effect. These agents do not reverse or antagonize the effects of other full agonists given simultaneously. Codeine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, levorphanol, methadone, morphine, oxycodone, oxymorphone, tapentadol and tramadol are classified as full agonists with hydrocodone, tramadol and tapentadol often considered weak, full opioid-agonists.[1,2,53] Morphine, the oldest opioid, originally extracted from poppy straw or opium remains the opioid agent against which all analgesics are compared.[1,2]

Tramadol has a dual mechanism of analgesic action. Low affinity binding of the parent compound and higher binding of the O-demethylated metabolite to mu-opioid receptors produces analgesia, while also inhibiting the reuptake of norepinephrine and serotonin in the central nervous system.[54,55]

Xartemis XR™ is formulated to immediately release a portion of its oxycodone and acetaminophen doses. Xartemis XR™ is designed to swell in gastric fluid and gradually release the remaining oxycodone and acetaminophen to the upper gastrointestinal (GI) tract.[56]

Non-steroidal anti-inflammatory drugs (NSAIDs) reversibly inhibit the enzyme cyclooxygenase, also referred to as prostaglandin endoperoxide synthase or COX. The COX enzyme exists as two isoforms, COX-1 and COX-2 and serves to mediate prostaglandin and thromboxane A2 production. In the setting of pain, COX inhibitors modify inflammatory and nociceptive responses. Aspirin acts to irreversibly block COX-1 activity.[54,57]

Acetaminophen has no activity at COX-1 or COX-2 receptors and possesses no anti-inflammatory activity. The exact mechanism of action of acetaminophen in mediating pain remains unknown, although it is postulated to inhibit prostaglandin synthesis in the central nervous system.[54,57]

Butalbital is a short-to-intermediate-acting barbiturate which depresses the sensory cortex, decreases motor activity and alters cerebellar function to produce drowsiness, sedation, hypnosis and dose-dependent respiratory depression.[54,57]

Caffeine inhibits phosphodiesterase and increases levels of 3'5'-cyclic AMP, acts as a CNS stimulant increasing medullary sensitivity to carbon dioxide, stimulates central inspiratory drive, diaphragmatic contractility and acts as a smooth muscle relaxant.[54,57]

Adjunctive Evidence

The ability of codeine and caffeine to increase the analgesic potency of aspirin was evaluated in a systematic review and meta-analysis by Zhang et al.[58] Codeine increased aspirin analgesia slightly, but the results were not clinically meaningful for the outcome of total pain relief (TOTPAR), while other outcome measures did not favor the combination. Caffeine was ineffective to increase aspirin analgesia.

At one time it was believed that combination analgesics containing caffeine promoted analgesic overdosage.[59] A review of the literature found no evidence to suggest caffeine associated with analgesic overdosage. Instead, phenacetin, which was also incorporated in combination analgesic preparations, was implicated. Phenacetin produced psychotropic properties and pharmacokinetic investigations support that phenacetin drug seeking behaviors may have produced the overdoses seen in patients receiving caffeine-containing products. Caffeine is a useful analgesic adjuvant at doses above 65 mg in the treatment of headache.[60] The addition of caffeine to analgesics increases the number of patients who become headache free (rate ratio 1.36, 95% CI 1.17 to 1.58). Caffeine also increases the number of patients reporting nervousness and dizziness (RR 1.60, 95% CI 1.26 to 2.03). No data suggests caffeine implicated in the phenomena of rebound headache with long-term use.

Trials demonstrate additivity in the use of combination hydrocodone and ibuprofen in the management of postoperative pain.[61]

Pharmacokinetics

The pharmacokinetics of the combination opioid agents is presented in *Table 4*. Most opioids have active metabolites. Renal elimination of unchanged drug and active- and inactive-metabolites is the most common mechanism of elimination. The combination of tramadol and acetaminophen affords a more rapid onset than tramadol alone and longer duration of analgesia than acetaminophen alone.[62] Codeine is metabolized to morphine via hepatic CYP2D6. Rapid and ultrarapid metabolizers are at risk of morphine toxicity (see *Special Populations*). Changes to the medication regimen should be undertaken only when a steady state (3 to 5 half-lives) has been achieved with special attention to renal and hepatic function as well as in the geriatric population where drug exposures may be greater, resulting in an increased risk of adverse events.

Table 4: Pharmacokinetics[54,56,63-65]

	Absorption	Distribution	Metabolism Active Metabolite	Excretion	Elimination Half-Life
Butalbital & ACTM & Caffeine & Codeine	Butalbital: well absorbed ACTM: BA 85-98% Caffeine: Well absorbed Tmax < 1 hr Codeine: Tmax: 60 min	Butalbital: PB 45% ACTM: PB 10-25% Codeine: PB: 7-25% V_D 3-6 L/kg	Butalbital: Hepatic ACTM: Hepatic Caffeine: Hepatic Codeine: Hepatic vis CYP2D6, CYP3A4, UDP pathways *Morphine*	Butalbital: Renal ACTM: Renal Caffeine: Renal Codeine: Renal	Butalbital: 35 hr ACTM: 1.25-3 hr Caffeine: 3 hr Codeine: 3 hr
Butalbital & Aspirin & Caffeine & Codeine	Each well absorbed Butalbital Tmax: 1.5 hr Aspirin Tmax: 40 min Caffeine Tmax < 1 hr Codeine Tmax: 60 min	Butalbital: PB 45% Salicylic Acid: PB 50-80% Codeine PB: 7-25% V_D 3-6 L/kg	Butalbital: Hepatic Aspirin: Hepatic Caffeine: Hepatic Codeine: Hepatic vis CYP2D6, CYP3A4, UDP pathways *Morphine*	Butalbital: Renal Aspirin: Renal Caffeine: Renal Codeine: Renal	Butalbital: 35 hr Aspirin: 12 min Caffeine: 3 hr Codeine: 3 hr
Carisoprodol & Aspirin & Codeine	Carisoprodol Onset: 30 min BA: unknown Tmax: 1.7 hr Aspirin Tmax: 1-2 hr Codeine Tmax: 60 min	Carisoprodol Duration: 4-6 hr Aspirin: Widely distributed Codeine PB: 7-25% V_D 3-6 L/kg	Carisoprodol: Hepatic via CYP2C19 *Meprobamate* Aspirin: Hepatic Codeine: Hepatic vis CYP2D6, CYP3A4, UDP pathways *Morphine*	Carisoprodol: Renal and Non-Renal Aspirin: Renal Codeine: Renal	Carisoprodol 2.0 hr *meprobamate 9.6 hr* Aspirin 15 min *salicylic acid 6 hr* Codeine: 3 hr

	Absorption	Distribution	Metabolism Active Metabolite	Excretion	Elimination Half-Life
Codeine & Acetaminophen	Both well absorbed Codeine Tmax: 1-1.5 hr Acetaminophen Tmax: 1 hr adult 0.5 hr pediatric	No information for combination product Codeine: PB: 7-25% Vd: 3-6 L/kg Acetaminophen PB: 10-25% V_D 0.7-1 L/kg	Codeine: Hepatic, first-pass, demethylation *Morphine* Acetaminophen: Hepatic	Codeine: Renal Acetaminophen: Renal	Codeine: 2.5-3 hr Acetaminophen: 1-4 hr
Dihydrocodeine & Acetaminophen & Caffeine	Dihydrocodeine BA: 20% Tmax: 1.6-1.8 hr	Dihydrocodeine: Not defined	Dihydrocodeine: Hepatic by CYP2D6 and CYP3A4 *nordihydrocodeine, dihydromorphine*	Dihdrocodeine: Renal	Dihydrocodeine: 4 hr
Dihydrocodeine & Aspirin & Caffeine	Dihydrocodeine BA: 20% Tmax: 1.6-1.8 hr	Dihydrocodeine: Not defined	Dihydrocodeine: Hepatic by CYP2D6 and CYP3A4 *nordihydrocodeine, dihydromorphine*	Dihdrocodeine: Renal	Dihydrocodeine: 4 hr
Hydrocodone & Acetaminophen	BA: well absorbed Onset: 10-20 min Tmax 1.3 hr	Hydrocodone Duration: 4-8 hr	Hydrocodone: Hepatic conjugation, CYP2D6, CYP3A4 *6-α and 6-β hydroxy metabolites, hydromorphone, Norhydrocodone* Acetaminophen: Hepatic	Hydrocodone: Renal Acetaminophen: Renal	Hydrocodone 3.8 hr ACTM 1.25 to 3 hours

	Absorption	Distribution	Metabolism Active Metabolite	Excretion	Elimination Half-Life
Hydrocodone & Ibuprofen	HC: Well absorbed Onset: 10-20 min Tmax: 1.7 hr IBU: Rapid BA: 80%	Duration: 4-8 hr Hydrocodone PB: 19-45% IBU: V_D 0.12-2 L/kg PB 99%	Hydrocodone: Extensive via CYP2D6, CYP3A4 *Hydromorphone* Ibuprofen: Hepatic	Hydrocodone: Renal Ibuprofen: Renal	Hydrocodone: 4.5 hr IBU: 2.2 hr
Oxycodone & Acetaminophen	Oxycodone Onset: 30 min BA: 60-87% Tmax: 3 hr ACTM: Well absorbed Onset: 10-15 min Tmax: 1 hr	Oxycodone: PB 45% V_D 211 L Acetaminophen: PB 20-50% V_D 0.9 L/kg Duration: 3-6 hr	Oxycodone: Extensive via CYP3A4 *noroxycodone, oxymorphone* ACTM: Extensive	Oxycodone: Renal ACTM: Renal	Oxycodone: IR: 3.51 hr Oxycodone ER: 4.5-5.4 hr ACTM IR: 4.1 hr ACTM XR 5.8-6.9 hr
Oxycodone & Aspirin	Oxycodone: BA 87%	Oxycodone: PB 45% V_D 211 L/kg Aspirin: PB: Variable	Oxycodone: Extensive via CYP2D6, N-dealkylation, O-demethylation, first-pass metabolism *noroxycodone, oxymorphone* Aspirin: Hepatic	Oxycodone: Renal Aspirin: Renal	Oxycodone 3.51 hr Aspirin: 2-3 hr
Oxycodone & Ibuprofen	Rapidly absorbed Tmax: Oxycodone 1.3-2.1 hr Ibuprofen 1.6-3.1 hr	Oxycodone: PB 45% Ibuprofen: 99%	Oxycodone: Extensive via CYP2D6, N-dealkylation, O-demethylation, first-pass metabolism *noroxycodone, oxymorphone* Ibuprofen: Hepatic	Oxycodone: Renal Ibuprofen: Renal	Oxycodone: 3.1-3.7 hr Ibuprofen: 1.8-2.6 hr

	Absorption	Distribution	Metabolism Active Metabolite	Excretion	Elimination Half-Life
Tramadol & Acetaminophen	Tramadol BA: 75%	Tramadol PB: 20% V_D 2.6-2.9 L/kg Acetaminophen PB: 20% V_D 0.9 L/kg	Tramadol: Hepatic via CYP2D6, CYP3A4 and conjugation *Metabolite M1 (O-desmethyltramadol)* Acetaminophen: Conjugation, oxidation by CYP2E1, CYP1A2, CYP3A4	Tramadol: Renal ACTM: Renal	ACTM: 2-3 hr

Key: ACTM=acetaminophen; BA=bioavailability; ER=extended release; IR=immediate release; PB=protein binding; Tmax=time to maximum concentration; V_D=volume of distribution; XR=extended release

Special Populations

Table 5 presents the special population information for the combination opioid products.

Geriatrics[54,64,66]

Updated 2015 Beers Criteria by the American Geriatric Society (AGS) recommend avoiding tramadol in geriatric patients with a creatinine clearance below 30 mL/min due to adverse central nervous system (CNS) effects. Immediate release tramadol should be used at a reduced dose and the extended-release formulation should be avoided. Tramadol should be with stable seizure disorders only when other agents have failed because it lowers the seizure threshold. The AGS recommends avoiding the use of barbiturates (e.g. butalbital) due to a higher rate of physical dependence, tolerance to sleep benefits and a greater risk of overdose at low dosages. NSAIDs (Ibuprofen) and aspirin (>325 mg/day) should be avoided in patients with a history of gastric or duodenal or gastric ulcers unless other agents have failed and gastroprotective agents are prescribed. NSAIDs should be avoided with creatinine clearance < 30 mL/min to avoid acute kidney injury or a further decline in renal function. NSAID-containing opioid products should not be used chronically unless other agents have failed and if used, concomitant gastroprotective agents may be appropriate. NSAIDs should not be used in patients with heart failure as they promote fluid retention and exacerbate heart failure. Skeletal muscle relaxants (carisoprodol) should be avoided in the elderly due to the poor tolerability of these highly anticholinergic medications, development of sedation, increased risk of fractures and a lack of evidence supporting a clinical benefit at dosages tolerated in the elderly. Opioids should be avoided in geriatric patients with a history of falls or fractures except for acute use following a fracture or joint replacement. When opioids are used in the elderly, the total number of CNS-active drugs should be limited to no more than three to reduce the risk of falls.

Pediatrics[54,64]

Dosage recommendations for children are lacking for these products. Most recommend adult dosing in adolescents. Aspirin containing products are contraindicated in children <12 years of age and adolescents who have or are recovering from chickenpox or flu-like symptoms to avoid the risk of Reye's syndrome. Codeine and dihydrocodeine are contraindicated for postop adenoidectomy or tonsillectomy pain especially in children with sleep apnea. Respiratory depression and death have occurred in pediatric ultra-rapid metabolizers of codeine due to a CYP2D6 polymorphism (see below *Codeine 2D6 Metabolizer Status).*

Renal Dysfunction[54,57,67]

Use of opioids in renal dysfunction should be undertaken with caution. The 3-glucuronide metabolite of hydrocodone can accumulate leading to neuroexcitatory effects. Oxycodone parent and metabolites can accumulate causing toxic and CNS-depressant effects. Codeine metabolites may accumulate causing adverse effects. The dosing interval of immediate release tramadol should be extended and the extended release product should be avoided at creatine clearance below 30 mL/min. In dialysis, oxycodone and codeine should not be used.

Hepatic Dysfunction[54,57,67]

Codeine and aspirin should be avoided in severe liver disease. Oxycodone, hydrocodone and acetaminophen containing products should be used cautiously. Tramadol dosages should be reduced in patients with cirrhosis.

Pregnancy[54,57]

Full-dose aspirin (≥300 mg/dose) and ibuprofen containing products carry pregnancy category D labeling, while all other agents are pregnancy category C. Ibuprofen should be avoided at 30-weeks of gestation and beyond to prevent premature closure of the ductus arteriosus.

Neonatal Opioid Withdrawal Reaction[54,64,68]

Pregnant mothers receiving prolonged use of opiates may place the neonate at risk of a withdrawal reaction. The syndrome may be life-threatening.

Breastfed Infants[54,64,68,69]

Codeine is secreted into breast milk in low, dose dependent concentrations. Ultrarapid metabolizers may secrete much higher concentrations of morphine into breast milk resulting in dangerously high morphine levels in the newborn. An opioid poisoning fatality was reported in the infant of a mother receiving codeine, who was an ultrarapid metabolizer, prompting the FDA to label codeine only for use in children above 2 years of age. The administration of codeine directly to a child who is an ultrarapid metabolizer places the child at increased risk of toxicity.

Codeine 2D6 Metabolizer Status[69,70]

The Clinical Pharmacogenetics Consortium developed guidelines for CYP450 genotype and codeine therapy in 2014. The CYP2D6*x2x genotype varies widely. It is present in 16-28% of North Africans, Ethiopian and Arabs, 2% in African Americans, 1-10% in Caucasians, 0.5-1% in Hispanics, and 0.5-1% in Chinese and Japanese persons. Codeine metabolism phenotypes are categorized as ultrarapid, extensive, intermediate or poor. Individuals with the CYP2D6*x2x genotype metabolize codeine to its active metabolite (morphine) more rapidly and completely than other people resulting in higher than expected concentrations of serum morphine levels. In the general population 1-2% of people are ultrarapid metabolizers[71] and make up to 75% more morphine than normal. It is strongly recommended that ultrarapid metabolizers avoid codeine as they produce significantly higher levels of morphine with risk of significant respiratory depression. The recommended alternatives include morphine and nonopioid analgesics. Tramadol, hydrocodone and oxycodone are not recommended as their metabolism is affected by CYP2D6 activity (effects greater with tramadol > hydrocodone or oxycodone). Extensive metabolizers (77-92% of the population)[71] should be dosed according to product labeling. Intermediate metabolizers (2-11% of the population)[71] produce less morphine and may have a reduced response to codeine therapy. If this occurs morphine or a nonopioid is recommended. Finally, poor metabolizers (5-10% of the population)[71] produce insufficient morphine to produce pain relief and codeine should be avoided in these patients due to a lack of efficacy. Alternatives

include morphine and nonopioid analgesics. Although best documented with codeine use in pediatrics, ultrarapid metabolizer toxicity and poor metabolizer inefficacy is possible with any opioid metabolized via CYP2D6 pathways (e.g. dihydrocodeine, hydrocodone, oxycodone and tramadol). Opioids should always be initiated at the lowest expected efficacious dose with close monitoring.

Table 5: Special Populations[54,64,66]

	Renal	Hepatic	Pregnancy	Lactation Crosses Placenta	Pediatric	Geriatric
Butalbital & ACTM & Caffeine & Codeine	No recommendation Use caution with severe impairment	No recommendation Use caution with severe impairment	C	Yes Consider the risk: benefit of therapy	Not established	Initiate at lower end of the dosage range Beers Criteria: Avoid Use
Butalbital & Aspirin & Caffeine & Codeine	No recommendation Use with caution	No recommendation Use with caution	C	Yes Consider the risk:benefit of discontinuing medication or breast feeding	Not established Reye syndrome risk	Initiate therapy at the lower dosage range Beers Criteria: Avoid Use
Carisoprodol & Aspirin & Codeine	No recommendation Not studied Use with caution	No recommendation Not studied Use with caution	D	Yes Carisoprodol at 2-4 times maternal plasma concentrations Recommended to avoid use because of aspirin (salicylate) content and bleeding risk for infant and codeine ultra-rapid metabolism risk of morphine toxicity	Not established in those < 16 years of age	Not established in those > 65 years of age Beers Criteria: Avoid Use
Codeine & Acetaminophen	No recommendation Not studied Use with caution	No recommendation Not studied Use with caution	C	Yes Consider the risk: benefit of therapy	Contraindicated for postop pain from tonsillectomy or adenoidectomy	Beers Criteria: Avoid use in elderly with a history or falls or fractures

	Renal	Hepatic	Pregnancy	Lactation Crosses Placenta	Pediatric	Geriatric
				Codeine ultra-rapid metabolism risk of morphine toxicity		
Dihydrocodeine & Acetaminophen & Caffeine	No recommendation Not studied Use with caution	No recommendation Not studied Use with caution	C	Yes Consider the risk:benefit of discontinuing medication or breast feeding	Not established Contraindicated for postop pain from tonsillectomy or adenoidectomy Caution with obstructive sleep apnea	Beers Criteria: Avoid use in elderly with a history or falls or fractures
Dihydrocodeine & Aspirin & Caffeine	No recommendation Not studied Use with caution	No recommendation Not studied Use with caution	No Info	Yes Consider the risk:benefit of discontinuing medication or breast feeding	Age ≤ 12 years: Avoid Contraindicated for postop pain from tonsillectomy or adenoidectomy Caution with obstructive sleep apnea	Use with caution Insufficiently studied in age ≥ 65 years Initiate at low end of dosing range Beers Criteria: Avoid use in elderly with a history or falls or fractures

	Renal	Hepatic	Pregnancy	Lactation Crosses Placenta	Pediatric	Geriatric
Hydrocodone & Acetaminophen	No adjustment	Use with caution Low dose well tolerated with dysfunction/cirrhosis. Toxicity has occurred at ACTM doses ≤ 4 gm/day. Avoid chronic use	C	Yes Consider the risk:benefit of therapy	Titrate to effect	Initial: 2.5-5 mg every 4-6 hours Beers Criteria: Avoid use in elderly with a history or falls or fractures
Hydrocodone & Ibuprofen	No recommendations Not studied Not recommended with advanced renal disease	No recommendations Not studied Use with caution with severe dysfunction	C	Yes Consider the risk:benefit of discontinuing medication or breast feeding	Age ≥ 16 years	Use with caution Use reduced doses Beers Criteria: Avoid use in elderly with a history or falls or fractures
Oxycodone & Acetaminophen	Extended-release: Initiate with 7.5 mg/325 mg and titrate; monitor for respiratory depression	Extended-release: Initiate with 7.5 mg/325 mg and titrate; monitor for respiratory depression	C	Yes Manufacturer does not recommend breast feeding	Initiate dosing based on oxycodone dose; MAX dose based on ACTM content	Extended-release: Use with caution Beers Criteria: Avoid use in elderly with a history of falls or fracture
Oxycodone & Aspirin	Use with caution CrCl < 10 mL/min: Avoid	Use with caution Severe impairment: Avoid	B (OXY) D (ASA)	Yes Consider the risk:benefit of discontinuing medication or breast feeding Caution: Reye Syndrome risk potential	Do Not Use	Refer to adult dosing Beers Criteria: Avoid use in elderly with a history or falls or fractures

	Renal	Hepatic	Pregnancy	Lactation Crosses Placenta	Pediatric	Geriatric
Oxycodone & Ibuprofen	No recommendations Not studied Avoid use in advanced disease	No recommendations Not studied Use caution with severe impairment	C D*	Yes Consider the risk:benefit of discontinuing medication or breast feeding	Age ≥ 14 years	Initiate therapy at lower dosage range Beers Criteria: Avoid use with history of falls or fractures
Tramadol & Acetaminophen	CrCl < 30 mL/min • Increase interval to every 12 hours MAX: 2 tabs every 12 hr	Avoid	C	Unknown Risk cannot be ruled out	Not established	Beers Criteria: Avoid use especially with concomitant history of epilepsy, seizures, fall or fracture

Key: *= at ≥30-weeks gestation; ASA=aspirin; OXY=oxycodone; CrCl=creatinine clearance; ACTM=acetaminophen; MAX=maximum dosage

Methods

A comprehensive review of the literature was performed to identify comparative evidence addressing the safety and efficacy of combination opioid products. For the clinical efficacy section, only clinical trials published in English evaluating efficacy of combination opioid agents in pain disorders or tension headache with reduction of pain as the endpoint were included. Trials evaluating the combination opioids as monotherapy or combination therapy where adjunctive medications remained constant throughout the trial are included. Trials comparing combination therapy with monotherapy opioid regimens, nonopioids or placebo were excluded. Trials included in systematic reviews were not individually evaluated.

An Information Scientist developed search strategies using keywords and controlled vocabulary (e.g. MeSH (NLM), EMTREE (EMBASE)) for the databases listed below. Validated RCT filters were used to restrict retrieval to clinical trials. A separate search for systematic reviews was also conducted. Neither date nor language limits were applied. Searches were conducted the week of October 26; 2016 Full search strategies are available in *Appendix 1*.

Two authors (VF and JF) performed a critical evaluation of the literature to identify relevant articles. Disagreements were discussed and solved by consent.

Results

We identified 2018 unique citations (2734 gross less 716 duplicates). A total of 59 systematic reviews and 167 randomized controlled trials were included for further evaluation. Excluded studies were performed in normal volunteers[72-75], for treatment of migraine headache[76-80] or for treatment of cancer pain[81-86]. Studies were excluded if the active opioid moiety of the combination was not of interest for this report[58,87-170]. Trials were excluded if the primary outcome measure was not pain reduction.[74,75,115,171-176] Dose ranging trials were excluded[177,178] as well as trials available in abstract form only[179-185]. Other reasons for exclusion, included the lack of full text availability[186 104,164,187-241], inclusion of the randomized control trial in an included systematic review[242-245], duplicate reports[27,109,246,247], study presented in a Letter to the Editor[248], and study erratum[249]. Some non-clinical evidence was captured for use in the manuscript, including background information[59,250-262], guidelines[27] and review articles[263-267].

Evidence:

Evidence reviewed for this report included 3 systematic reviews/meta-analyses and 15 randomized controlled trials. The most common efficacy measures were (SPID) the sum of pain intensity differences, (PPID) peak pain intensity difference, (TOTPAR) total pain relief, (PPR) peak pain relief, (SPRID) sum of TOTPAR and SPID, (PRS) pain relief scores, time to/or percent achievement of 50% pain relief, need for rescue analgesia, mean/median time to remedication, (NNT) number needed to treat for an additional beneficial outcome, (MeP) mean pain reduction in the last week, (PR) pain at rest, (PM) pain with movement, (BDI-II) Beck Depression inventory and functional status relating to the ability to perform activities of daily living. Pain was commonly assessed via a (VRS) verbal rating scale of 0-4 (no pain to

excruciating pain). Comparative evidence was not found for acetaminophen/butalbital/caffeine/codeine, aspirin/carisoprodol/codeine, dihydrocodeine/acetaminophen/caffeine, dihydrocodeine-aspirin/caffeine or oxycodone/aspirin.

Aspirin + Butalbital + Caffeine + Codeine

One systematic review and 2 RCTs evaluated aspirin-butalbital-Caffeine-codeine (ABCC).[268,269,270] The systematic review by Au et al[270] assessed combination analgesics for post-operative pain following third molar surgery. A total of 3521 patients from 14 systematic reviews/meta-analyses were included. For aspirin containing regimens (aspirin + caffeine; aspirin + codeine; ABCC), ABCC was found more efficacious for efficacy endpoints of TOTPAR and SPID at 6 hours. MacDonald et al[269] reported on 90 patients with 188 episodes of post-surgical pain treated with ABCC or acetaminophen 325 mg + codeine 30 mg (AC). Efficacy was determined by patient assessment of pain severity and relief. For all pain severities, treatments were superior to placebo ($p<0.001$). In severe pain, ABCC was statistically superior to AC ($p<0.001$) while in moderate pain, the treatments did not differ. When all pain episodes were pooled (moderate and severe), ABCC was significantly more efficacious than AC ($p<0.025$). Desjardins et al[268] reported on 123 patients treated with a single dose of AC or ABCC following outpatient dental surgery. Patients took a dose of analgesic when pain intensity reached moderate to severe. For all measures of analgesic efficacy, ABCC was numerically but not statistically superior to AC. For measures of anxiety and relaxation, both AC and ABCC were superior to placebo. In comparison to placebo, ABCC was significantly superior for measures of TOTPAR, PPR and global assessment of analgesia. AC was superior to placebo for global assessment of analgesia only. No safety differences were noted between treatments. The evidence suggests that ABCC is overall superior to AC for analgesia in postsurgical patients. Investigators suggest the increased efficacy relates to a reduction in anxiety.

Acetaminophen + Tramadol

One systematic review and 5 RCTs evaluated the analgesic efficacy of acetaminophen + tramadol (AT).[271-276] The systematic review by Moore et al[271] included 39 Cochrane reviews including 460 studies and involving 50,000 patients who received a single dose of a combination analgesic in patients with moderate to severe postoperative pain. Non-Cochrane tramadol reviews of high quality were included separately. The primary outcome measure was the given or calculated relative risk (RR) and number needed to treat (NNT) to achieve 50% maximum pain relief over 4-6 hours compared with placebo. Treatment with AT (acetaminophen 650 mg + tramadol 75 mg) resulted in a relative risk of 12 (95% CI, 6.4 to 21) and number needed to treat of 2.9 (95% CI 2.5-3.5). Relative risk scores ranged for other treatments from 2.6 for acetaminophen 600/650 mg + codeine 60 mg to 6.3 for acetaminophen 800/1000 + codeine 60 mg. NNT ranged from 1.8 for acetaminophen 1000 mg + oxycodone 10 mg to 3.9 for acetaminophen 600/650 mg + codeine 60 mg. Indirect comparison of the results (comparing confidence intervals) suggests that AT may be less effective than acetaminophen600/650 + codeine 60 mg, ibuprofen 400 mg + oxycodone 5 mg and acetaminophen 650 mg + oxycodone 10 mg or acetaminophen 1000 mg + oxycodone 10 mg.

Alfano et al[276] compared acetaminophen 325 + tramadol 37.5 mg (AT) with acetaminophen 500 mg + codeine 30 mg (AC) in 121 patients undergoing day surgery. For the primary outcome verbal rating score (VRS) for pain AT was superior to AC at 6 and 12 hrs (p<0.01) and at 24 and 48 hours (p<0.001). Fewer patients receiving AT received rescue medication (18% vs 5.5%). No differences were found between groups for quality of life measures. Adverse events were more common with AC (62.1% vs 36.4%, p=0.008). Smith et al[273] compared the analgesic efficacy of acetaminophen 325 mg + tramadol 37.5mg (AT), acetaminophen 300 mg + codeine 30 mg (AC) and placebo in the treatment of 305 abdominal or orthopedic surgery patients with at least moderate post-surgical pain. Patients received 2 tablets of study medication followed by 1 or 2 tablets every 4 to 6 hours for six days. For all primary outcome measures during the first 4 hours post-dose, no differences were found between AT and AC for outcomes of TOTPAR, SPID or SPRID. During this 4-hour assessment period, AT was superior to placebo in all measures while AC did not differ from placebo for any measure. For secondary efficacy measures, AT was superior to placebo in all measures (average daily pain relief, average daily pain intensity, final visit pain intensity, final visit pain relief) while AC did not differ from placebo in any measure. The mean daily dosage of active treatments was similar. No statistical differences were found between active treatments for any secondary efficacy measures. Discontinuations due to a lack of efficacy were similar between active treatments. AC was associated with a higher frequency of constipation, vomiting and discontinuation due to adverse events than AT. One serious adverse event (constipation) was associated with AC therapy. Fricke et al[275] compared the analgesic efficacy of acetaminophen + tramadol, acetaminophen + hydrocodone and placebo in 200 adult patients having extraction of at least 2 impacted 3rd molars. When pain became moderate-to-severe, patients received a single dose of either acetaminophen 325 mg + tramadol 37.5 mg (AT1), or acetaminophen 650 mg + tramadol 75 mg (AT2), or acetaminophen 650 mg + hydrocodone 10 mg (AH), or placebo. Responses were recorded for 0-4 hr, 4-8 hr and 0-8 hr. For the primary outcome measures of TOTPAR, SPID and SPRID AT1 and AH performed statistically better than placebo at each time period (p<0.024). The 3 active treatments did not differ from each other over any time period. AT1 differed from placebo only during the 0-4-hour period. A dose-response was found with the tramadol containing combinations. Secondary endpoint analysis demonstrated a longer duration of pain relief with high dose tramadol and hydrocodone containing products. Remedication was required earlier with placebo than active treatments (p<0.001). Patients global assessment of the medications found active treatment superior to placebo (p<0.001). More patients receiving the low-dose tramadol regimen or placebo required supplemental analgesia during the 8-hour trial, however, during the 0-2 hr window low-dose tramadol was numerically superior to placebo (54% vs 84%). Treatment emergent adverse events occurred in 42% of patients and were more common with AH and placebo therapy than either the high- or low-dose tramadol regimens (56%, 48%, 34%, 30%, respectively). Nausea and vomiting was 50% more common with AH than AT therapy. Hewitt et al[274]compared the analgesic efficacy of acetaminophen 650 mg + tramadol 75 mg (AT), acetaminophen 650 mg + hydrocodone 7.5 mg (AH), and placebo in 603 adults with an acute ankle sprain. Patients were given a dose of study medication in the urgent care center or emergency department and discharged with a 5-day supply of medication to be taken up to four times daily. Primary outcome measures included analgesia within 4 hours,

SPID, SPRID and the percent of patients achieving 30% and 50% pain relief. For all measures active treatment (AT or AH) was statistically superior to placebo and the two treatments did not differ. Post hoc assessment found the two active treatments met non-inferiority criteria. Over days 1-5, AH was superior to placebo for average and final pain relief. AT was superior to placebo for average pain relief. Measures of average and final pain intensity did not differ between the 3 treatment groups. Efficacy failures ranged from 11.2% with placebo to 2.5% with AH. An assessment of time to efficacy failure found AH superior to placebo with all other comparisons not statistically significant. Adverse events and discontinuations due to adverse events were similar between active treatments and numerically higher than placebo. Mullican et al[272] evaluated the analgesic efficacy of acetaminophen 325 mg + tramadol 37.5 mg (AT) with acetaminophen 325 mg + codeine 30 mg (AC) in adults with chronic, nonmalignant low back pain, osteoarthritis pain or both. A total of 462 patients were randomized 2:1 for AT and AC. No significant differences in efficacy measures were found between groups for measures of TOTPAR, SPID or pain relief at 30 minutes and 6 hours. Patient and investigator assessments of efficacy were comparable as were the mean and maximum daily doses. The types of adverse events were comparable in both groups with AC treatment associated with a significantly higher rate of somnolence and constipation than AT.

Overall, acetaminophen + tramadol performed similarly to acetaminophen + codeine and acetaminophen + hydrocodone in a variety of settings including dental surgery, outpatient surgery, ankle sprain and chronic pain. Efficacy may not be equivalent to combination analgesics containing stronger opioids (e.g. oxycodone) however, head-to-head data is not available and the evidence is insufficient to answer this with specificity. In most studies, acetaminophen + tramadol vs acetaminophen + codeine yielded statistical superiority to placebo in efficacy outcome measures more regularly. Acetaminophen + tramadol appears to be better tolerated (e.g. fewer adverse events) than acetaminophen + codeine.

Ibuprofen + Oxycodone

Two systematic reviews[270,271] compared the analgesic efficacy of ibuprofen + oxycodone. Au et al[270] performed a systematic review of post-operative 3rd molar extraction pain. The identified 14 placebo-controlled, RCTs with a minimal sample size of 15 patients who received one of 17 analgesic combination regimens (10 groups). A total of 3521 patients were included who received one of the following regimens; acetaminophen (ACTM) 600/650 mg + codeine 60 mg; ACTM 300 mg + codeine 30 mg; ACTM 1 gm + codeine 30 mg; ACTM 1 gm + hydrocodone (HC) 10 mg; ACTM 500 mg + HC 7.5 mg; ACTM 325 mg + oxycodone (OXY) 5 mg; ACTM 500 mg + ibuprofen (IBU) 200 mg; ACTM 1 gm + IBU 400 mg; aspirin (ASA) 650 mg + caffeine 65 mg; ASA 650 mg + codeine 60 mg; ASA 325 mg + caffeine 40 mg + butalbital 50 mg + codeine 15 mg; IBU 200 mg + caffeine 200 mg; IBU 200 mg + caffeine 100 mg; IBU 200 mg + caffeine 50 mg; IBU 400 mg + codeine 25.6 mg or IBU 400 mg + OXY 5 mg. A meta-analysis was performed using a random effects model. The data was found to be homogenous with less than moderate heterogeneity. The combination of IBU 400 mg + OXY 5 mg was found superior to all other regimens at 6-hour measurements of SPID (6.44; range for all drugs 1.46 to 6.44) and TOTPAR of (9.31; range for all drugs 3.24 to 10.3). Adverse events reflected those

expected with opioid therapy: nausea, vomiting, dizziness, drowsiness and headache. IBU 400 mg + OXY 5 mg resulted in a prevalence of drowsiness of 13.25%. Other adverse effects related to OXY occurred at a low prevalence 90.4-2.4%). Overall, regimens containing more potent opioids and those with higher acetaminophen dosages were associated with a higher frequency of adverse events. In the review of systematic reviews performed by Moore et al[271] (see above) efficacy measures included RR and NNT to produce a 50% reduction in pain. They further calculated a susceptibility to publication bias score (number of treated patients reporting a null effect needed to produce a clinically insignificant effect of a NNT>10). The review included 41 different analgesic agents or combinations (see Appendix 1 for specific products). Data was stratified to low risk of publication bias or some risk of publication bias. The relative risk and number needed to treat for 50% maximal pain relief over 4 to 6 hours compared to placebo yielded similar numbers (with overlapping confidence intervals) for the combination opioid products. Relative risk ranged from 1.5 to 20). Number needed to treat ranged from 1.5 to 12. The time to remedication was longest with oxycodone combination products (~ 10 hr) and shortest with codeine combination products (~ 4 hr).

Overall, ibuprofen + oxycodone is at least as efficacious and likely more efficacious than other analgesic combinations, with a longer duration of analgesia and a higher risk of drowsiness.

Ibuprofen + Hydrocodone

Four randomized controlled trials compared the efficacy of ibuprofen + hydrocodone (IH) with acetaminophen + codeine (AC) or acetaminophen + oxycodone (AO). Ziccardi et al[277] compared the analgesic efficacy of a single-dose of ibuprofen 400 mg + hydrocodone 15 mg with acetaminophen 600 mg + codeine 60 mg or placebo in 125 patients with postoperative pain following third molar extractions. Mean pain relief scores were statistically higher with IH than AC starting 2-hours post-dose and extending for 8 hours. Pain intensity difference scores were higher (better analgesia) with IH vs AC achieving statistical significance after 1.5 hours (p<0.05). There was no difference between active treatments in the time to meaningful pain relief. The time to remedication (duration of analgesia) was statistically longest with IH than AC (5.50 hr vs 3.03 hr, p<0.001). Patients mean global evaluation of analgesic efficacy was significantly higher with IH than other treatments. The incidence and type of adverse events did not differ between active treatments.

The remaining three randomized, controlled trials were pharmaceutical company sponsored and performed by the same group of investigators.[278-280] In 147 patients with acute, moderate-to-severe, acute low back pain, ibuprofen 200 mg + hydrocodone 7.5 mg (IH) was compared with acetaminophen 325 mg + oxycodone 5 mg (AO).[279] One tablet of the study medication was prescribed every 4-6 hours as needed for pain with a daily maximum of 5 tablets. No difference was found between treatment groups for measures of mean daily pain relief score, mean daily number of tablets of study medication, mean daily number of doses of study medication, mean daily number of tablets/doses of supplemental analgesic, global evaluation,

short-form health survey (SF-36), or incidence or type of adverse events. A second trial[280] compared the analgesic efficacy of ibuprofen 400 mg + hydrocodone 15 mg with acetaminophen 650 mg + oxycodone 10 mg or placebo in 180 postoperative obstetric or gynecologic surgery patients with moderate to severe pain. Efficacy measures were not different during the first four hours of treatment. For efficacy measures beyond 4 hours (PRS, SPID and TOTPAR) IH was statistically superior to AO ($p<0.05$ for each measure). No difference between active treatments were found for secondary outcomes (see Appendix I). Adverse events occurred in a similar number of patients and reflected known opioid side effects. The third trial[278] compared the analgesic efficacy of two different doses of ibuprofen + hydrocodone (200 mg/7.5 mg and 400 mg/15 mg) with acetaminophen 600 mg + codeine 60 mg in the treatment of chronic pain over 4-weeks. Most patients had chronic back, arthritic or musculoskeletal pain. Medications were administered every 6 to 8 hours as needed. For the efficacy measures of PRS, mean number of daily doses of study medication and mean number of daily supplemental analgesics the higher dose IH regimen performed statistically superior to each of the other treatments ($p\leq0.05$). Global assessment scores favored the higher dose IH regimen at weeks 1,2 and 4 ($p\leq0.05$). For all efficacy variables lower dose IH and AC performed similarly. Discontinuation rates due to unsatisfactory analgesic response were significantly higher for AC than higher dose IH dosage (7.5% vs 1.3%, $p\leq0.05$). An equivalent number of patients in each treatment group experienced adverse events during the study. Higher dose IH was associated with statistically higher incidence of nausea, dizziness, pruritus and sweating than the other two treatments ($p\leq0.05$). Diarrhea was significantly more common with AC than either IH regimen. Dyspepsia rates were significantly lower with higher dose IH regiments. Significantly more patients discontinued therapy with higher- vs lower-dose IH regimens.

Overall, doses of ibuprofen + hydrocodone within the FDA prescribing recommendations of 10 mg/dose resulted in efficacy similar to acetaminophen + oxycodone and acetaminophen + codeine. The acetaminophen component of the combination analgesic was greater than the currently marketed 325 mg per tablet/capsule which may confound the results. Additionally, the superiority of the higher dose hydrocodone regimen (ibuprofen 400 mg + hydrocodone 15 mg) likely reflects the higher than FDA approved hydrocodone dosage of 15 mg that extends the duration of action due to pharmacokinetic and not true efficacy factors. Evidence does not support the superiority of the currently available and approved dosage regimen of ibuprofen + hydrocodone over acetaminophen + codeine or acetaminophen + oxycodone.

Acetaminophen + Oxycodone

Three systematic reviews compared the analgesic efficacy of acetaminophen + oxycodone (AO) with acetaminophen + codeine (AC).[270,271,281] One of the systematic reviews also includes acetaminophen + hydrocodone (AH) as a comparator. Four randomized, controlled trials yield additional evidence.[247,280,282,283] Comparators include acetaminophen + hydrocodone (1 trial), acetaminophen + codeine (2 trials) and ibuprofen + hydrocodone (1 trial, see Palangio 2002, above).

The systematic review by Au et al[270]compared 17 different analgesic combination regimens for post-operative, third molar surgery pain (see Appendix 1).Treatment with

acetaminophen 325 mg + oxycodone 5 mg (AO) was not superior to other regimens for any analgesic outcome measure. Treatment with AO was associated with 41% of patients complaining of nausea. In the systematic review performed by Moore et al[271] single dose oral analgesic therapy for moderate to severe postoperative pain was evaluated for 39 Cochrane reviews of ~50,000 patients. Efficacy measures of risk ratio and number needed to treat to achieve 50% maximal pain relief compared to placebo resulted in overlapping confidence intervals for all opioid combination products. Although not a primary outcome measure, nor of statistical significance, the time to remedication was longest with oxycodone combination products (~ 10 hr) and shortest with codeine combination products (~ 4 hr). A systematic review by Mkontwana et al[281] included 8 RCTS of 962 patients receiving oral analgesia or placebo for post-caesarean pain. All trials were of small size with high heterogeneity and only four trials had a low level of bias. No studies reported on the primary outcome measure 'adequate pain relief'. For the outcome measure, 'additional analgesia needed' No differences were found between treatments (opioids, non-opioids or combination analgesics) or placebo. Subgroup analysis evaluating the need for additional pain relief found no difference found no difference between AO and placebo (RR 1.0, 95% CI 0.78 to 1.28, one trial, 96 women). Treatment with combination opioid products resulted in a higher incidence of adverse events than placebo (RR 13.18, 95% CI 2.86 to 60.68, three trials, 252 women). Corsinovi et al[283] compared the analgesic efficacy of acetaminophen 325 mg + oxycodone 5mg (AO), acetaminophen 500 mg + codeine 30 mg (AC) or conventional therapy (acetaminophen, NSAIDs, COX2-inhibitors alone or in combination) in 154 nursing home females with severe osteoarthritis-related pain, sub-optimally responsive to conventional treatments. At 6-weeks, AC and AO were statistically superior to conventional therapies, and not different from each other, for measurements of pain reduction, pain at rest, pain with movement, cognitive function changes or depressive symptoms. Adverse event rates, withdrawals due to adverse events and discontinuation rates were not statistically different between groups. Two RCTs using the same protocol were performed by the same investigators[247,282] The first trial[247] compared the analgesic efficacy of acetaminophen 325 mg + oxycodone 5 mg (AO) to acetaminophen 325 mg + hydrocodone 5 mg (AH) in 240 adult patients with acute musculoskeletal extremity pain discharged from the emergency department. Patients were given a prescription for a 3-day supply of a combination opioid and received a followup phone call ~24 hours after discharge. Patients assessed their level of pain before their most recent opioid dose and 2 hours following the dose. The numerical pain rating scale score (NRS) before and after opioid were not different between treatments. The mean difference in NRS between treatment groups did not meet the *a priori* threshold for clinical relevance (NRS of 1.3). Both opioid combinations resulted in a 50% reduction in pain score. Adverse events were similar between groups. Treatment with AO resulted in non-significant 10% higher rates of nausea and dizziness than AH. The second trial[282] compared acetaminophen 325 mg + oxycodone 5 mg to acetaminophen 300 mg + codeine 30 mg in 240 patients. Mean decreases in pain scores, percent achieving 50% pain relief, patient satisfaction scores and adverse events were not statistically different between groups. The authors suggest that acetaminophen + codeine has the benefit of a less restrictive schedule (Schedule V) than acetaminophen + oxycodone (Schedule II) with lower abuse potential.

Overall, evidence does not support a difference in efficacy or safety for oxycodone + acetaminophen vs other comparators (AH, AC, IH).

Acetaminophen + Hydrocodone

One systematic review[270] and four RCTs[275,274,247,284] evaluate the analgesic efficacy of acetaminophen and hydrocodone (AH). In the systematic review by Au et al[270] acetaminophen + hydrocodone was one of 17 analgesic combinations evaluated in the treatment of 3rd molar surgery post-operative pain. The combination of acetaminophen (500-1000 mg) + hydrocodone (7.5-10 mg) was found less effective than ibuprofen (400 mg) and oxycodone (5 mg) for 6-hour mean SPID (2.89 to 3.7 vs 6.44, respectively) and mean TOTPAR (4.51 to 7.2 vs 9.31, respectively). AH regimens resulted in higher rates of nausea, dizziness, headache and drowsiness than ibuprofen/oxycodone regimens.

Fricke et al[275]found no differences between low or high doses of acetaminophen + tramadol (AT) and AH for efficacy outcome measures. Treatment emergent adverse events (nausea, vomiting) were twice a common with AH vs AT therapy. Hewitt et al[274] found non-inferiority between AT or AH for primary outcome efficacy measures with no difference in analgesic failure rates, time to failure between treatments or discontinuation rates due to adverse events. In the two studies performed by Chang et al[247,284] efficacy outcome measures were similar for AH and AO, and for AH and acetaminophen + codeine (AC). AO was associated with 10% more nausea and dizziness than AH while no difference in adverse events were noted between AH and AC.

Overall, evidence does not support a difference in efficacy or safety for acetaminophen + hydrocodone vs other comparators (AH, AT).

Acetaminophen + Codeine

Acetaminophen and codeine (AC) was a comparator in 13 of the 18 evidence studies included in this report.[268-273,276-278,281-284] The doses of AC in the studies ranged from AC 300 mg/30 mg to AC 1000 mg/60 mg. Four trials compare AC with acetaminophen + tramadol (AT). Overall, evidence from 1 systematic review[271] and 3 RCTs[249,272,273] suggests that AC is equivalent to AT for measures of pain relief while associated with a higher incidence of adverse events. Two RCTs compared AC with ibuprofen + hydrocodone (IH).[277,278] One trial assessed post-operative pain and the other chronic pain. Both trials found IH superior to AC for analgesia with one trial finding more discontinuations due to a lack of analgesia with AC. Although oxycodone is more potent that codeine, three meta-analysis[270,271,281] and two RCTs[282,283] failed to find a significant difference between AC and AO for efficacy outcomes or adverse events.. One systematic review[270] found no difference between AC or acetaminophen + butalbital + caffeine + codeine (ABCC) for efficacy or adverse events. One RCT[268] found AC inferior to ABCC for analgesia and anxiety and a second trial[269] found AC inferior to ABCC for severe pain but not significantly different for the treatment of moderate pain. AC and ibuprofen + oxycodone (IO) were comparators in two systematic reviews.[270,271] One review found IO superior to other comparators, including AC[270]; the second systematic review found no significant differences among combination opioid comparators.[271] Finally, no differences in efficacy or safety were

found between AC and acetaminophen + hydrocodone in one systematic review[270] and one RCT[284]

Overall, evidence may suggest that AC is a weaker combination opioid product than comparators. Safety evidence is insufficient to find AC different than IH, AT, AO, ABCC, IO or AH.

Additional info

The combination opioid agents are not indicated for cancer pain or for long-term use. However, these agents may be used in this setting. A systematic review of NSAIDs with or without opioids for cancer pain found only short-term studies with significant heterogeneity in methods and outcomes. At best a slight statistical advantage for combination therapy vs either single agent was found in some studies.[81] Currently, evidence is inadequate to support the use of combination opioid agents for cancer pain.

Of interest, some evidence found NSAIDs statistically superior to acetaminophen + codeine for treatment of dental pain. A meta-analysis evaluating the effects of nonopioid medications for dental pain included 33 placebo controlled, randomized, double-blind, parallel study design trials of 5171 patients having third molar extraction from 1975 to August 1996.[285] Studies evaluated pain using categorical pain scales. Outcomes were summed pain intensity differences, including summed pain intensity difference (SPID), peak pain intensity differences (PPID), total pain relief (TOTPAR) or peak pain relief (PPAR). Pooled evidence found no differences between nonopioid medications and Tylenol® with Codeine. Further analysis considering only full analgesic doses of nonopioids found efficacy was statistically superior for NSAIDS (ibuprofen, diflunisol, ketorolac, flurbiprofen) compared to the combination of acetaminophen (600-650 mg) with codeine (60 mg).

Evidence does not support the superiority of one combination opioid preparation over another.

Safety

Black Box Warnings[54,57,68]

All agents carry a black box warning for concomitant use with benzodiazepines or other CNS depressants. Preparations containing NSAIDs place the patient at risk of gastrointestinal and cardiovascular toxicity; acetaminophen for hepatotoxicity; and codeine and dihydrocodeine for morphine toxicity in ultrarapid metabolizers. With the exception of products containing tramadol, carisoprodol or butalbital, all agents carry warnings for abuse, misuse, addiction potential; life threatening respiratory depression; accidental ingestion; and neonatal opioid withdrawal syndrome. Codeine/acetaminophen elixir carries a medication error warning.

Acetaminophen hepatotoxicity

The Acute Liver Failure Study Group found acetaminophen responsible for 40% of cases of liver failure and one third of the deaths in the US.[286] Combination prescription medications, particularly acetaminophen-opioid combinations were implicated. Most overdoses were

unintentional and resulted from the use of the combination opioid-acetaminophen analgesic with the use of additional over-the counter-products containing acetaminophen for fever, cold or pain.

A review article assessed the evidence of acetaminophen-opioid combination induced hepatotoxicity as well as the consequences of removing these products from the US market following an FDA advisory committee vote of 20-17 to eliminate these products in 2009.[287] The authors found no denominator-based studies of adequate statistical design to allow for an estimate of whether these products present a substantial risk to the public. If these products were discontinued patients currently stabilized would require alternative therapy, potentially associated with different toxicities (e.g. NSAID use and gastrointestinal toxicity). Health care effects would range from affecting pain management and patient's quality of life to possible increases in healthcare utilization and costs. Among a number of alternative considerations the author's proposed a reduction in the acetaminophen content in acetaminophen-opioid combination products.[287]

Duh et al[266] accessed an insurance claims database of more than 1 million persons for people with a claim for acetaminophen + oxycodone or acetaminophen + hydrocodone to assess the risk of acetaminophen hepatotoxicity-related hospitalizations. The daily initial acetaminophen dosage was ≥2500 mg for 66% of patients and ≥4000 mg for 19.9% of patients. Pretreatment and post-treatment differences achieved statistical significance at a two-sided alpha level of 0.05 but they did not consider this reliable due to the large sample size, inconsistency in time trends, small magnitude of risk differences (1-2 per 10,000) and lack of difference between opioid only and opioid-acetaminophen treatment groups.

The FDA assessed the evidence supporting the use of larger vs smaller doses of acetaminophen in combination products and found a lack of clinical trial evidence. In 2011 the Center for Drug Evaluation and Research of the Food and Drug Administration instructed manufacturers of opioid combination products to limit the dose of acetaminophen per dosage to 325 mg. Labeling was updated so that all acetaminophen containing opioid products now carry a Black Box safety warning that describes the risk of severe liver injury with use of acetaminophen.[288]

Table 6 presents a complete list of the black box warnings assigned to these medications. *Table 7* presents the contraindications and warnings associated with the medications.

Table 6: Black Box Warnings[54,55,64,68]

Black Box Warning	Description	Preparations
Addiction, Abuse, Misuse (Appropriate Use)	Opioids expose patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing and monitor all patients regularly for the development of these behaviors or conditions	Codeine/acetaminophen Dihydrocodeine/acetaminophen/caffeine Hydrocodone/acetaminophen Hydrocodone/ibuprofen Oxycodone/acetaminophen Oxycodone/aspirin Oxycodone/ibuprofen

Life-Threatening Respiratory Depression	serious, life-threatening, or fatal respiratory depression may occur. Monitor for respiratory depression, especially during initiation of or following a dose increase	Codeine/acetaminophen Dihydrocodeine/acetaminophen/caffeine Hydrocodone/acetaminophen Hydrocodone/ibuprofen Oxycodone/acetaminophen Oxycodone/aspirin Oxycodone/ibuprofen
Accidental Ingestion	Accidental ingestion of even one dose, especially by children, can result in a fatal overdose.	Codeine/acetaminophen Dihydrocodeine/acetaminophen/caffeine Hydrocodone/acetaminophen Hydrocodone/ibuprofen Oxycodone/acetaminophen Oxycodone/ibuprofen Oxycodone/aspirin
Neonatal Opioid Withdrawal Syndrome	Prolonged use of opioids during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.	Codeine/acetaminophen Dihydrocodeine/acetaminophen/caffeine Hydrocodone/acetaminophen Hydrocodone/ibuprofen Oxycodone/acetaminophen Oxycodone/ibuprofen Oxycodone/aspirin
Cytochrome P450 3A4 Interaction	The concomitant use of cytochrome P450 3A4 inhibitors may result in an increase in plasma concentrations, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in the plasma concentration. Monitor patients receiving any CYP3A4 inhibitor or inducer	Codeine/acetaminophen Dihydrocodeine/acetaminophen/caffeine Hydrocodone/acetaminophen Oxycodone/acetaminophen Oxycodone/ibuprofen Oxycodone/aspirin
Hepatotoxicity	Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed 4000 milligrams per day, and often involve more than one acetaminophen-containing product	Codeine/acetaminophen Codeine/butalbital/acetaminophen/caffeine Dihydrocodeine/acetaminophen/caffeine Hydrocodone/acetaminophen Oxycodone/acetaminophen Tramadol/acetaminophen
Warning: Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants	Concomitant use of opioids with benzodiazepines or other CNS depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of opioids with benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation.	Codeine/acetaminophen Codeine/butalbital/acetaminophen/caffeine Codeine/butalbital/aspirin/caffeine Codeine/carisoprodol/aspirin Dihydrocodeine/acetaminophen/caffeine Dihydrocodeine/aspirin/caffeine Hydrocodone/acetaminophen Hydrocodone/ibuprofen Oxycodone/acetaminophen Oxycodone/ibuprofen Oxycodone/aspirin Tramadol/acetaminophen
Cardiovascular Risk	NSAIDs increase the risk of serious and potentially fatal cardiovascular thrombotic events, including myocardial infarction and stroke; risk may occur early in therapy and may increase with duration of use; contraindicated for coronary artery bypass graft peri-operative pain	Hydrocodone/ibuprofen Oxycodone/ibuprofen
Serious Gastrointestinal Bleeding,	NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events, including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and	Hydrocodone/ibuprofen Oxycodone/ibuprofen

Ulceration And Perforation	without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events.	
Ultra-Rapid Metabolism Of Codeine To Morphine	Respiratory depression and death have occurred in children who received codeine following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine due to a cytochrome P450 2D6 (CYP2D6) polymorphism.	Codeine/acetaminophen Codeine/butalbital/acetaminophen/caffeine Codeine/butalbital/aspirin/caffeine Codeine/carisoprodol/aspirin Dihydrocodeine/acetaminophen/caffeine Dihydrocodeine/aspirin/caffeine
Risk of Medication Errors	Ensure accuracy when prescribing, dispensing, and administering acetaminophen 120 mg/codeine 12 mg per 5mL. Dosing errors due to confusion between mg and mL, and other acetaminophen/codeine oral suspensions of different concentrations can result in accidental overdose and death.	Codeine/acetaminophen (liquid)

Table 7: Combination Opioid Medication Cautions and Precautions [54,55,64,68]

	Cautions and Precautions
Codeine + Acetaminophen	Hypersensitivity to drug/class/component; respiratory depression; paralytic ileus; post tonsillectomy/adenoidectomy in pediatrics; abrupt withdrawal with long-term use; sulfite hypersensitivity (branded tablet); G6PD deficiency; pediatrics; geriatrics; debilitated patients; ultra-rapid CYP2D6 metabolizer; severe renal/hepatic impairment; pulmonary impairment; sleep apnea with long-term use; CNS depression, CNS depressant use; alcohol use; alcohol/drug abuse history; head injury; increased ICP; seizure disorder; acute abdomen; GI/GU obstruction; hypothyroidism; adrenal insufficiency; biliary disease; urethral stricture; prostatic hypertrophy.
Codeine + Butalbital + ACTM + Caffeine	Hypersensitivity to drug/class/component; post-tonsillectomy/adenoidectomy in pediatrics; abrupt withdrawal with long-term use; elderly patients; hepatic impairment; renal impairment; increased intracranial pressure, history of drug abuse, pulmonary impairment, sleep apnea with long-term use, ultra-rapid CYP2D6 metabolizer; concomitant CNS depressants; alcohol use; G6PD deficiency
Codeine + Butalbital + Aspirin + Caffeine	Hypersensitivity to drug/class/component; ASA or NSAID-induced asthma/urticaria; aspirin triad, peptic ulcer disease; porphyria; GI bleeding; coagulation disorder; uncontrolled hypertension; G6PD deficiency; febrile viral infection if < 20 years of age; post-tonsillectomy/adenoidectomy in pediatrics; abrupt withdrawal with long-term use; ultra-rapid CYP2D6 metabolizer; thrombocytopenia, surgery/trauma, intracranial lesion, increased intracranial pressure, history of GI bleed, gastro-esophageal reflux disease (GERD), gout with high aspirin intake, history of drug abuse, concomitant CNS depressant use; alcohol use; renal impairment; hepatic impairment; sleep apnea with long-term use; elderly patients; debilitated patients
Codeine + Carisoprodol + Aspirin	Hypersensitivity to drug/class/component; hypersensitivity to meprobamate/felbamate; acute/intermittent porphyria; ASA or NSAID-induced asthma/urticaria; aspirin triad; coagulation disorder; GI bleeding, uncontrolled hypertension, G6PD deficiency; febrile viral infection if < 20 years of age; post-tonsillectomy/adenoidectomy in pediatrics; abrupt withdrawal with long-term use; more than 3 alcoholic drinks daily; ultra-rapid CYP2D6 metabolizer; pediatrics; geriatrics; debilitated; renal impairment; hepatic impairment; seizure history/risk; history of substance abuse or risk; concomitant CNS depressants; PUD; history of GI bleeding; GERD; acute pancreatitis/biliary disease; acute abdomen; thrombocytopenia; pulmonary disease; hypotension; dehydration; increased ICP; surgery/trauma; intracranial lesion; gout with high ASA intake
Dihydrocodeine + Acetaminophen + Caffeine	Hypersensitivity to drug/class/component; severe respiratory depression; acute/severe asthma; hypercarbia; paralytic ileus; post-tonsillectomy/adenoidectomy use in pediatrics; abrupt withdrawal with long-term use; geriatric; debilitated patients; ultra-rapid CYP2D6 metabolizer;

	renal/hepatic/pulmonary impairment; sleep apnea with long-term use; CNS depression, concomitant CNS depressants; alcohol use; delirium tremens; history of substance abuse; increased ICP; seizure disorder, circulatory shock; hypotension; hypovolemia; acute abdomen; acute pancreatitis/biliary disease; prostatic hypertrophy; urethral stricture; hypothyroidism; adrenal insufficiency; chronic malnutrition; changes to smoking habit.
Dihydrocodeine + Aspirin + Caffeine	Hypersensitivity to drug/class/component: ASA/NSAID-induced asthma/urticaria; aspirin triad, severe respiratory depression, acute/severe hypercapnia or asthma; GI bleeding; coagulation disorder; paralytic ileus; uncontrolled hypertension; G6PD deficiency; febrile viral infection if < 20 years of age; post-tonsillectomy/adenoidectomy in pediatrics; abrupt withdrawal with long-term use; thrombocytopenia; coagulation disorder; PUD; history of GI bleed; GERD; COPD; pulmonary impairment; sleep apnea with long-term use; CNS depression; surgery/trauma; intracranial lesion; increased ICP; seizure disorder; hypotension; hypovolemia; acute abdomen; severe inflammatory bowel disease; gallbladder disease; pseudomembranous colitis; hepatic/renal impairment; ultra-rapid CYP2D6 metabolizer; prostate hypertrophy; urethral stricture; history of drug abuse; alcohol use; hypothyroidism; adrenal insufficiency; gout with high ASA intake; changes to smoking habit; geriatric; debilitated.
Hydrocodone + Acetaminophen	Hypersensitivity to drug/class/component; abrupt withdrawal with long-term use, geriatric; debilitated patients; hepatic/renal/pulmonary impairment; history of drug abuse; alcohol use; concomitant CNS depressants; sleep apnea with long-term use; head injury; increased intracranial pressure; acute abdomen; hypothyroidism; Addison's disease; prostate hypertrophy; urethral stricture; G6PD deficiency.
Hydrocodone + Ibuprofen	Hypersensitivity to drug/class/component; ASA/NSAID-induced asthma/urticaria; aspirin triad; respiratory depression; paralytic ileus; pregnancy at 30 weeks gestation; perioperative use in CABG surgery; abrupt withdrawal with long-term use; recent MI; cardiovascular disease or risk; hypertension; congestive heart failure; fluid retention; cor pulmonale; asthma/COPD; pulmonary impairment; sleep apnea for long-term use; acute abdomen; biliary disease; shock; CNS depression; head injury; increased ICP; seizure disorder; history or risk of GI bleed or ulcer; coagulation disorder; geriatric; debilitated patients; severe renal/hepatic impairment; alcohol/drug abuse; hypothyroidism; adrenal insufficiency; urinary tract obstruction.
Oxycodone + Acetaminophen	Hypersensitivity to drug/class/component; respiratory depression; acute/severe asthma; hypercarbia; paralytic ileus; abrupt withdrawal with long-term use; hypersensitivity to sulfites (capsule); circulatory shock; renal/hepatic/pulmonary impairment; sleep apnea with long-term use; CNS depression; head injury; intracranial lesion; increased ICP; seizure disorder; delirium tremens; toxic psychosis; toxic psychosis; history of drug abuse; alcohol use; acute alcoholism; kyphoscoliosis; acute abdomen; biliary disease; prostatic hypertrophy; urethral stricture; hypothyroidism; myxedema; Addison's disease; postoperative use; G6PD deficiency; geriatric; debilitated patients.
Oxycodone + Aspirin	Hypersensitivity to drug/class/component; ASA/NSAID-induced asthma/urticaria; aspirin triad; GI bleed; coagulation disorder, uncontrolled hypertension; paralytic ileus; G6PD deficiency; severe respiratory depression; hypercarbia; acute/severe asthma; febrile viral illness if < 20 years of age; abrupt withdrawal with long-term use; 3 or more alcohol drinks daily; pulmonary disease; sleep apnea with long-term use; CNS depression; intracranial lesion; surgery/trauma increased ICP; thrombocytopenia; seizure disorder; hypovolemia; circulatory shock; PUD; history of GI bleed; GERD, acute abdomen; biliary disease; thyroid disorder; toxic psychosis; adrenal insufficiency, gout with high-ASA use; renal/hepatic impairment; geriatric; debilitated patients.
Oxycodone + Ibuprofen	Hypersensitivity to drug/class/component; ASA/NSAID-induced asthma/urticaria; aspirin triad; history of angioedema; respiratory depression; hypercarbia; acute/severe asthma; paralytic ileus; pregnancy at 30 week gestation; perioperative CABG surgery; abrupt withdrawal with long-term use; recent MI; cardiovascular disease or risk; hypertension; congestive heart failure; fluid retention; asthma/COPD; cor pulmonale; sleep apnea with long-term use; pulmonary impairment; acute abdomen; biliary disease; shock; CNS depression, head injury, increased ICP, seizure disorder, history/risk for GI bleed/ulcer; coagulation disorder; geriatric; debilitated patients; severe renal/hepatic impairment; alcohol/drug abuse; hypothyroidism; adrenal insufficiency; urinary tract infection.
Tramadol + Acetaminophen	Hypersensitivity to drug/class/component or opioids; hepatic impairment; acute alcohol/drug intoxication; suicidal behavior/ideation; addiction history; abrupt withdrawal with long term use;

	geriatrics; pediatrics; ultra-rapid CYP2D6 metabolizer; renal impairment; seizure history or risk; head injury; increased ICP; sleep apnea with long-term use; respiratory depression; concomitant respiratory/CNS depressants; alcohol use; psychiatric disorder; acute abdomen; G6PD deficiency.

Key: ASA=aspirin; CNS=central nervous system; G6PD=glucose-6-phosphate dehydrogenase; GERD=gastroesophageal reflux disease; GI=gastrointestinal; GU=genitourinary; ICP=intracranial pressure; NSAID=nonsteroidal anti-inflammatory drug; PUD=peptic ulcer disease

Adverse Events

The most common adverse effects associated with the opioid analgesics include nausea, vomiting, sedation, pruritus and constipation. Serious adverse effects frequently reported with opioid use include respiratory depression, urinary retention, hypotension and delirium. *Table 8* compares the adverse effects associated with the combination opioid agents.

Xartemis XR™

Barrett et al[258]reported on the safety of immediate-release/extended release oxycodone/acetaminophen tablets (Xartemis XR™) from 9 phase 1 trials in healthy volunteers and 2 phase 3 trials (N=1106). Adverse events occurring at greater than 10% were pruritus, nausea, vomiting, dizziness, headache and somnolence. The frequency was similar to immediate-release oxycodone monotherapy but higher than tramadol-acetaminophen. The adverse event profile was similar to other opioids.

Table 8: Adverse Drug Reactions

	Codeine-Acetaminophen	Codeine-Acetaminophen-Butalbital-Caffeine	Codeine-Carisoprodol-Aspirin	**Dihydrocodeine**-Acetaminophen-Caffeine	Dihydrocodeine-Aspirin-Caffeine	Hydrocodone-Acetaminophen	Hydrocodone-Ibuprofen	Oxycodone-Acetaminophen	Oxycodone-Aspirin	Oxycodone-Ibuprofen	Tramadol-Acetaminophen
CNS	Dizziness, drowsiness, dysphoria, euphoria, sedation, serotonin syndrome. somnolence	Agitation, confusion, depression, dizziness, drowsiness, euphoria, excitement, fatigue, headache, intoxication, lethargy, numbness, paresthesia, sedation, seizure, shakiness	Agitation, ataxia, drowsiness, depressive reactions, dizziness, headache, irritability, sedation, vertigo	Dizziness, drowsiness, sedation	>10% dizziness, drowsiness, sedation 1-10% drug dependence, increased ICP	Anxiety, clouding of consciousness, coma, dizziness, drowsiness, drug dependence, dysphoria, euphoria, fear, lethargy, malaise, mental deficiency, mood changes, sedation, stupor	>10% Headache, drowsiness, dizziness 1-10% Anxiety, insomnia, nervousness, thinking abnormality, confusion, hypertonia, pain, paresthesia	>10% Dizziness 1-10% Headache, drowsiness, fatigue, insomnia, dysphoria	Dizziness, drowsiness, dysphoria, euphoria, sedation	>10% Dizziness, drowsiness 2-10% headache	1-10% Drowsiness, dizziness, insomnia, anxiety, confusion, euphoria, fatigue, headache, nervousness
CV		Syncope, tachycardia	Syncope, tachycardia, hypo-tension, facial flushing		1-10% Bradycardia, hypotension, palpitations, peripheral vasodilation	Bradycardia, cardiac arrest, circulatory shock, hypotension	1-10% Edema, palpitations, vasodilation	1-10% Peripheral edema, circulatory depression, hypotension, shock	Circulatory depression, hypotension, shock	2-10% Vasodilation	
Derm	Pruritus, rash	Hyperhidrosis, pruritus	Pruritus, urticaria, rash	Dermatologic reaction, pruritus	>10% Dermatologic reaction, pruritus	Cold/clammy skin, diaphoresis, pruritus, skin rash	1-10% Diaphoresis, pruritus	1-10% Skin rash, erythema, excoriation, pruritus, skin blister, erythematous dermatitis	Pruritus		1-10% Diaphoresis, pruritus, skin rash
Endo/ Metab	Adrenocortical insufficiency	Hot flash			1-10% Increased ADH release	Hypoglycemic coma	1-10% Increased thirst	1-10% Hot flash			1-10% Hot flash
GU		Diuresis			1-10% Ureteral spasm	Nephrotoxicity, ureteral spasm, urinary retention		1-10% Dysuria			1-10% Prostatic disease

	Codeine-Acetaminophen	Codeine-Acetaminophen-Butalbital-Caffeine	Codeine-Carisoprodol-Aspirin	**Dihydrocodeine**-Acetaminophen-Caffeine	Dihydrocodeine-Aspirin-Caffeine	Hydrocodone-Acetaminophen	Hydrocodone-Ibuprofen	Oxycodone-Acetaminophen	Oxycodone-Aspirin	Oxycodone-Ibuprofen	Tramadol-Acetaminophen
GI	Abdominal pain, constipation, nausea, vomiting	Abdominal pain, constipation, dysphagia, flatulence, heartburn, nausea, vomiting, xerostomia	Constipation, diarrhea, nausea, epigastric distress, gastritis, hiccup, occult bleeding, vomiting,	Constipation, nausea, vomiting	>10% Constipation, nausea, vomiting 1-10% biliary tract spasm	Abdominal pain, constipation, gastric distress, heartburn, nausea, occult blood in stools, peptic ulcer, vomiting	>10% Constipation, nausea, dyspepsia 1-10% Abdominal pain, diarrhea, flatulence, hiccups, vomiting, xerostomia, anorexia, gastritis, melena, oral mucosal ulcer	>10% Nausea 1-10% Vomiting, constipation, diarrhea, dyspepsia, xerostomia	Constipation, nausea, vomiting	>10% Nausea 2-10% Vomiting, constipation, diarrhea, dyspepsia, flatulence	
Heme/ Onc	Agranulo-cytosis, thrombo-cytopenia					Agranulo-cytosis hemolytic anemia, iron deficiency anemia, prolonged bleeding time, thrombo-cytopenia		1-10% Hemolytic anemia, neutropenia, pancytopenia, thrombo-cytopenia			
Hepatic	Liver failure					Hepatic necrosis, hepatitis		1-10% Increased liver enzymes			
HS	Yes	Yes	Angioedema Rash, Rhinorrhea, urticaria, Erythema multiforme, eosinophilia, fixed drug eruptions		1-10% Histamine release	Hyper-sensitivity reactions					
NMS		Leg pain, muscle fatigue				Vesicle sphincter spasm	1-10% Weakness			2-10% Weakness	1-10% Tremor, weakness
Ophth			Miosis		Miosis						

	Codeine-Acetaminophen	Codeine-Acetaminophen-Butalbital-Caffeine	Codeine-Carisoprodol-Aspirin	**Dihydrocodeine**-Acetaminophen-Caffeine	Dihydrocodeine-Aspirin-Caffeine	Hydrocodone-Acetaminophen	Hydrocodone-Ibuprofen	Oxycodone-Acetaminophen	Oxycodone-Aspirin	Oxycodone-Ibuprofen	Tramadol-Acetaminophen
Otic		Otalgia, tinnitus	tinnitus			Hearing loss in chronic, overdose	1-10% Tinnitus				
Renal						Renal tubular necrosis	1-10% Polyuria				
Resp	dyspnea	Dyspnea, nasal congestion			Respiratory depression	Airway obstruction, apnea, dyspnea, respiratory depression	1-10% Flu-like symptoms, dyspnea, pharyngitis, rhinitis	1-10% Cough, apnea, respiratory arrest, respiratory depression	Apnea, respiratory arrest, respiratory depression		
Misc		Fever, heavy eyelids					1-10% Infection, fever			2-10% Fever	
Other	Hypogonadism	Agranulocytosis, cardiac stimulation, dependence, erythema multiforme, hyperglycemia, hypogonadism, irritability, nephrotoxicity, rash, thrombocytopenia, TEN, tremor	Insomnia, idiosyncratic reactions,	Hypogonadism	Hypogonadism	Hypogonadism	Hypogonadism	Hypogonadism	Hypogonadism	Idiosyncratic hepatotoxicity, hypogonadism, increased liver enzymes, tachycardia, urinary retention, anxiety, hyperkinesia, hypertonia	Albuminuria, cardiac arrhythmia, depression, dyspnea, exacerbation of migraine, hypertension, hallucination, melena, oliguria, syncope, tachycardia, tongue edema, urinary retention, withdrawal reaction

Key: ADH=Antidiuretic hormone; CNS=central nervous system; CV=cardiovascular; Derm=dermatologic: Endo=Endocrine; GI=gastrointestinal; GU=genitourinary; Heme=hematologic; HS=hypersensitivity; ICP=intracranial pressure; Metab=metabolic; Misc=miscellaneous; NMS=neuromuscular system; Onc=oncologic; Ophth=Opthamologic; Other=rare or case reports; Resp=respiratory; TEN=toxic epidermal necrolysis

Drug Interactions[54,55,64,68,289]

Central nervous system depression may occur with any opioid when combined with other medications having these effects, including other narcotic analgesics, sedative-hypnotics, tranquilizers, tricyclic antidepressants, muscle relaxants, phenothiazines, general anesthetics or other agents with CNS depressant activity (e.g. alcohol). Severe respiratory depression, sedation, hypotension, coma and death have occurred. The addition of a partial-agonist or antagonist to an opioid analgesic may result in a loss of analgesia and/or the development of withdrawal symptoms. No opioid should be initiated within 14 days of stopping a monoamine oxidase inhibitor (MAOI) as the effects of the opioid may be significantly augmented. The use of concomitant anticholinergic drugs with opioids may result in urinary retention, severe constipation and paralytic ileus. The use of tramadol and other medications with serotonergic activity (e.g. selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, triptans or cyclobenzaprine) may result in the development of serotonin syndrome. Cytochrome P450 (CYP) isoenzymes affect the metabolism of a number of opioids. *Table 9* presents an overview of cytochrome P450 metabolic pathways.

Interactions with other medications often result in well documented effects;

- Acetaminophen may cause analgesic-associated nephropathy, methemoglobinemia and is affected as a CYP2E1 substrate.
- Aspirin may interact with other medications to cause analgesic-associated nephropathy, antiplatelet effects, gastrointestinal mucosal injury with bleeding risk, metabolic acidosis, uricosuric/anti-uricosuric effects, and changes in urinary pH.
- Butalbital may cause CNS depression, increase thyroid hormone clearance and affect hepatic microsomal enzyme metabolism. Butalbital is a major inducer of enzymatic pathways CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A4 a minor inducer of CYP1A2, CYP2E1 and inducer of UGT1A1 and UGT2B4.
- Caffeine may produce CNS stimulation and hypertensive effects. Caffeine is a moderate inhibitor of CYP1A2 and a substrate for CYP1A2 metabolic pathways.
- Carisoprodol may cause CNS depression and is a CYP2C19 substrate.
- Codeine may produce anticholinergic-like effects, CNS and/or respiratory depression and possesses weak serotonergic effects. Codeine is a substrate for CYP2D6 and CYP3A4 metabolic pathways.
- Dihydrocodeine may produce anticholinergic-like effects, CNS and/or respiratory depression, and weak serotonergic effects. Dihydrocodeine is a substrate for CYP2D6 metabolic pathways.

- Hydrocodone may produce anticholinergic-like effects, CNS and/or respiratory depression and weak serotonergic effects. Hydrocodone may prolong the QT interval and acts as a substrate for CYP2D6 and CYP3A4 metabolic pathways.
- Ibuprofen may interact with other medications to produce antiplatelet effects, hypertension, hyponatremia and decrease renal perfusion or renal function.
- Oxycodone may produce anticholinergic-like effects, CNS and/or respiratory depression and weak serotonergic effects. Oxycodone is a substrate for CYP2D5 and CYP3A4 metabolic pathways.
- Tramadol may lower the seizure threshold, produce CNS depression, and weak serotonergic effects. Tramadol acts as a substrate for CYP2B6, CYP2D6 and CYP3A4 metabolic pathways.

Table 9: Overview of P450 metabolic pathways

Metabolic Pathway Substrates	Inhibitor	Inducers
CYP3A4		
Alprazolam, amiodarone, amlodipine, aripirazole, astemizole, atorvastatin, buspirone, calcium channel blockers, carbamazepine, ciclosporin, cisapride, clarithromycin, codeine, dexamethasone, diazepam, dihydrocodeine, diltiazem, domperidone, erythromycin, estradiol, felodipine, fentanyl, finasteride, hydrocodone, hydrocortisone, indinavir, lercanidipine, losartan, methadone, midazolam, nelfinavir, nifedipine, pimozide, progesterone, ritonavir, saquinavir, sildenafil, simvastatin, tacrolimus, testosterone, tramadol, triazolam, verapamil, R-warfarin	amiodarone, cimetidine, clarithromycin, diltiazem, erythromycin, fluconazole, indinavir, itraconazole, ketoconazole, nefazadone, nelfinavir, ritonavir, saquinavir, verapamil, grapefruit juice	Butalbital, carbamazepine, efavirenz, nevirapine, oxcarbazepine, phenobarbital, phenytoin, pioglitazone, rifampicin, St John's Wort
CYP2D6		
Amitriptyline, carvedilol, chlorphenamine, chlorpromazine, clomipramine, codeine, desipramine, dextromethorphan, donepezil, duloxetine, fluoxetine, haloperidol, hydrocodone, imipramine, metoclopramide, metoprolol, nortriptyline, ondansetron, oxycodone, paroxetine, propranolol, risperidone, tamoxifen, thioridazine, timolol, tramadol, venlafaxine	Amiodarone, bupropion, celecoxib, cimetidine, citalopram, clomipramine, duloxetine, escitalopram, fluoxetine, haloperidol, indinavir, levomepromazine, paroxetine, quinidine, sertraline, terbinafine, ticlodipine	Rifampicin
CYP2C9		
Celecoxib, diazepam, diclofenac, fluoxetine, fluvastatin, glibenclamide, glimepride, glipizie, ibuprofen, irbesartan, losartan, meloxicam, naproxen, phenytoin, orsemide, tolbutamide, S-warfarin	Amiodarone, fluconazole, fluoxetine, fluvastatin, isoniazid, metronidazole, paroxetine, zarfilukast	Butalbital, phenobarbital, rifampicin, secobarbital
CYP1A2		
Acetaminophen, amitriptyline, clomipramine, clozapine, imipramine, theophylline, R-warfarin, caffeine, cyclobenzaprine, fluvoxamine, haloperidol, mexiletine, olanzapine, pentazocine, propranolol, tacrine	Amiodarone, caffeine (weak), cimetidine, ciprofloxacin, erythromycin, fluvoxamine	Butalbital, carbamazepine, omeprazole, rifampin, broccoli, brussel sprouts, cigarette smoking
CYP2C19		
Amitriptyline, carisoprodol, citalopram, clomipramine, diazepam, imipramine, lansoprazole, nelfinavir, omeprazole, phenytoin	Cimetidine, felbamate, fluoxetine, fluvoxamine, ketoconazole, lansoprazole, omeprazole, paroxetine, ticlodipine	Butalbital, carbamazepine, norethindrone, rifampin

Metabolic Pathway Substrates	Inhibitor	Inducers
CYP2E1		
Acetaminophen, chlorzoxazone, dapsone, ethanol, enflurane, halothane, isoflurane	Disulfuram	Butalbital, chronic ethanol, isoniazid, tobacco

Summary:

Overall, combination opioid analgesic agents are effective treatment options for acute pain disorders. We found no consistent evidence of differences between agents, although it would be expected that combinations containing more potent opioids are more efficacious. We found no evidence of substantial differences in adverse events between agents. The most common adverse effects associated with the opioid analgesics include nausea, vomiting, sedation, pruritus and constipation.

Consideration should be given to the whether carisoprodol/aspirin/codeine should be given preferred status, as guidelines recommend avoiding the combination of opioid with skeletal muscle relaxants, and there is a lack of evidence to support their efficacy. Xartemis XR™ provides the benefit of extended pain relief, although guidelines do not recommend the use of long-acting preparations for acute pain. Comparative evidence did not find a clear difference between codeine combinations and other agents; however, it is unclear whether preferred status is appropriate. Codeine combination products appears to be the weakest of all the agents, confer a significant risk in children, and the potential under-treatment of 25% of the population. Pain management must be individualized for each patient and include careful evaluation of patient history, age, comorbidities, type of pain, underlying diseases, concurrent medications and risk of abuse or misuse.

Appendix 1: Full Search Strategy

Medline: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>
1 ((acetaminophen$ or acetominophen$ or algotropyl or anacin or datril or panadol or paracetamol or tylenol or apap or acamol or acephen or acetaco or acetamidophenol* or Ascriptin or Aspercin or Aspir-low or aspirtab or buffasal or bufferin or buffinol or Durlaza or Ecotrin or Halfprin or asaphen or entrophen or novasen or "praxis asa" or "pro-AAS" or acetylsalicylic acid or acetysal or acylpyrin or aloxiprimum or colfarit or dispril or easprin or ecotrin or endosprin or magnecyl or micristin or polopirin or polopiryna or solprin or solupsan or zorprin or ibuprofen$ or brufen or ibumetin or motrin or nuprin or rufen or salprofen) adj3 (codein$ or hydrocodon$ or oxycodon$ or pentazocin$ or Carisoprodol$ or Tramadol$ or ardinex or isocodeine or "n-methylmorphine" or BUTALBITAL? or codinovo or dicodid or dihydrocod$ or hycodan? or hycon or hydrocodeinonebitartrate? or dihydrohydroxycod$ or dihydrone? or dinarkon or eucoda? or oxiconum? or oxycodeinon? or oxycone or oxycontin? or pancodin$ or theocodin? or percodan? or adolonta? or biodalgic? or biokanol? or contramal? or jutadol? or mtwtramadol? or nobligan? or prontofort? or takadol? or theradol? or tiral? or topalgic? or tradol? or tradolpuren? or tradonal? or tralgiol? or trama 1a pharma? or trama abz? or trama dorsch? or trama kd? or trama-dorsch? or tramabeta? or tramadin? or tramadoc? or tramadoldolgit? or tramadolhameln? or tramadolor? or tramadolratiopharm? or tramadorsch? or tramadura? or tramagetic? or tramagit? or tramake? or tramal? or tramex? or tramundin? or tranadik? or trasedal? or ultram? or xymel 50? or zamudol? or zumalgic? or zydol? or zytram? or fortral or lexir or pentazocine or talwin or carisoma? or carisoprodat? or isobamate? or isomeprobamate? or isopropylmeprobamate? or "mio relax?" or soma? or somalgit? or soprodol? or vanadomor?)).ti,ab,kw,kf,rn. [Set 1: Drug ADJACENT to Drug] (2468)
2 Acetaminophen/ or Aspirin/ or Ibuprofen/ (74385)
3 (acetaminophen$ or acetominophen$).ti,ab,rn,kw,kf. (25300)
4 (algotropyl or anacin or datril or panadol or paracetamol or tylenol or apap or acamol or acephen or acetaco or acetamidophenol*).ti,ab,rn,kw,kf. (13853)
5 Aspirin$.ti,ab,kw,kf,rn. (68568)
6 (Ascriptin or Aspercin or Aspir-low or aspirtab or buffasal or bufferin or buffinol or Durlaza or Ecotrin or Halfprin or asaphen or entrophen or novasen or "praxis asa" or "pro-AAS" or acetylsalicylic acid or acetysal or acylpyrin or aloxiprimum or colfarit or dispril or easprin or ecotrin or endosprin or magnecyl or micristin or polopirin or polopiryna or solprin or solupsan or zorprin).ti,ab,kw,kf,rn. (9817)
7 ibuprofen*.ti,ab,kw,kf,rn. (15319)
8 (brufen or ibumetin or motrin or nuprin or rufen or salprofen).ti,ab,kw,kf,rn. (292)
9 or/2-8 [NON-OPIOID ANALGESICS per P&T Protocol] (108871)
10 codeine/ or hydrocodone/ or oxycodone/ or pentazocine/ or Carisoprodol/ or Tramadol/ (12776)
11 CODEIN$.ti,ab,kw,kf,rn. (7328)
12 (ardinex or isocodeine or "n-methylmorphine").ti,ab,kw,kf,rn. (17)
13 BUTALBITAL?.ti,ab,kw,kf,rn. (191)
14 HYDROCOD$.ti,ab,kw,kf,rn. (1170)
15 (codinovo or dicodid or dihydrocod$ or hycodan? or hycon or hydrocodeinonebitartrate?).ti,ab,kw,kf,rn. (597)
16 OXYCODON$.ti,ab,kw,kf,rn. (3574)
17 (dihydrohydroxycod$ or dihydrone? or dinarkon or eucoda? or oxiconum? or oxycodeinon? or oxycone or oxycontin? or pancodin$ or theocodin? or percodan?).ti,ab,kw,kf,rn. (308)
18 TRAMADOL?.ti,ab,kw,kf,rn. (4885)
19 (adolonta? or biodalgic? or biokanol? or contramal? or jutadol? or mtwtramadol? or nobligan? or prontofort? or takadol? or theradol? or tiral? or topalgic? or tradol? or tradolpuren? or tradonal? or tralgiol? or trama 1a pharma? or trama abz? or trama dorsch? or trama kd? or trama-dorsch? or tramabeta? or tramadin? or tramadoc? or tramadoldolgit? or tramadolhameln? or tramadolor? or tramadolratiopharm? or tramadorsch? or tramadura? or tramagetic? or tramagit? or tramake? or tramal? or tramex? or tramundin? or tranadik? or trasedal? or ultram? or xymel 50? or zamudol? or zumalgic? or zydol? or zytram?).ti,ab,kw,kf,rn. (204)
20 PENTAZOCIN$.ti,ab,kw,kf,rn. (3293)
21 (fortral or lexir or pentazocine or talwin).ti,ab,kw,kf,rn. (3293)

22 CARISOPRODOL?.ti,ab,kw,kf,rn. (479)
23 (carisoma? or carisoprodat? or isobamate? or isomeprobamate? or isopropylmeprobamate? or "mio relax?" or soma? or somalgit? or soprodol? or vanadomor?).ti,ab,kw,kf,rn. (13436)
24 or/10-23 [OPIOID ANALGESICS per P&T Protocol] (32529)
25 (and/9,24) not 1 [SET 2: OPIATE & NON-OPIATE ANALGESICS] (995)
26 ((opioid? or opiate? or morphin$) adj4 (acet?minophen$ or aspirin? or ibuprofen? or tylenol? or advil or paracetamol?)).ti,ab,kw,kf,ot,rn. (1620)
27 exp Analgesics, Opioid/ (100285)
28 exp Analgesics, Non-Narcotic/ (298910)
29 Drug combinations/ (65594)
30 ((and/27-29) or 26) not (or/1,25) [Set 3: Broad Search: Opioids & Non-Opioids & Drug Combinations] (1637)
31 (randomized controlled trial or controlled clinical trial).pt. or randomi?ed.ti,ab. or placebo.ti,ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti. (1167281)
32 exp animals/ not humans.sh. (4331351)
33 31 not 32 [RCT Filter Cochrane precision and sensitivity maximizing] (1082390)
34 meta-analysis/ (74683)
35 cochrane.jw. (16346)
36 (meta analy$ or metaanaly$).ti,ab,pt,kw,kf. or (pooled adj2 analys$ adj4 (trial? or study or studies)).ti,ab. (130386)
37 ((systematic or scoping or integrative) adj3 review).ti,ab,jw,ot. (94444)
38 (overview or umbrella).ti. or ((overview or over view or scoping) adj2 review).ab. or scoping study.ti,ab. (35816)
39 (systematic adj3 synthesis).ti. (183)
40 review.pt. and (medline or pubmed or embase or cinahl or (cochrane adj2 (library or database or trial?))).ab. (92089)
41 or/34-40 [MF-SR filter] (263447)
42 (or/1,25) and 41 [Systematic Review Results-Focussed on specific drug combinations] (126)
43 ((or/1,25) and 33) not 42 [RCT Filter Results--focussed on specific drug combinations] (1152)
44 (30 and 41) not (or/42-43) [SR Results broader concepts opioids near aspirin etc] (59)
45 (30 and 33) not (or/42-44) [RCT Results broader concepts--Opioids & non opioids & Drug combination] (437)
46 or/42,44 [SR] (185)
47 from 46 keep 27-185 [ML-SRs to export] (159)
48 remove duplicates from 47 (140)
49 or/43,45 [RCT] (1589)
50 from 49 keep 193-1589 [ML RCT] (1397)
51 remove duplicates from 50 (1375)

	EMBASE.com October 26, 2016] NOTE: Missing line numbers are the result of EMBASE.com; no terms are missing.	
Set #	Search Terms	Results
13	((acetaminophen* OR acetominophen* OR algotropyl OR anacin OR datril OR panadol OR paracetamol OR tylenol OR apap OR acamol OR acephen OR acetaco OR acetamidophenol* OR ascriptin OR aspercin OR 'aspir-low' OR aspirtab OR buffasal OR bufferin OR buffinol OR durlaza OR ecotrin OR halfprin OR asaphen OR entrophen OR novasen OR 'praxis asa' OR 'pro-aas' OR 'acetylsalicylic acid' OR acetysal OR acylpyrin OR aloxiprimum OR colfarit OR dispril OR easprin OR ecotrin OR endosprin OR magnecyl OR micristin OR polopirin OR polopiryna OR solprin OR solupsan OR zorprin OR ibuprofen* OR brufen OR ibumetin OR motrin OR nuprin OR rufen OR salprofen) NEAR/3 (codein* OR hydrocodon* OR oxycodon* OR pentazocin* OR carisoprodol* OR tramadol* OR ardinex OR isocodeine OR 'n-methylmorphine' OR butalbital* OR codinovo OR dicodid OR dihydrocod* OR hycodan* OR hycon OR	2,354

	hydrocodeinonebitartrate* OR dihydrohydroxycod* OR dihydrone* OR dinarkon OR eucoda* OR oxiconum* OR oxycodeinon* OR oxycone OR oxycontin* OR pancodin* OR theocodin* OR percodan* OR adolonta* OR biodalgic* OR biokanol* OR contramal* OR jutadol* OR mtwtramadol* OR nobligan* OR prontofort* OR takadol* OR theradol* OR tiral* OR topalgic* OR tradol* OR tradolpuren* OR tradonal* OR tralgiol* OR 'trama 1a pharma*' OR 'trama abz*' OR 'trama dorsch*' OR 'trama kd*' OR 'trama-dorsch*' OR tramabeta* OR tramadin* OR tramadoc* OR tramadoldolgit* OR tramadolhameln* OR tramadolor* OR tramadolratiopharm* OR tramadorsch* OR tramadura* OR tramagetic* OR tramagit* OR tramake* OR tramal* OR tramex* OR tramundin* OR tranadik* OR trasedal* OR ultram* OR 'xymel 50' OR zamudol* OR zumalgic* OR zydol* OR zytram* OR fortral OR lexir OR pentazocine OR talwin OR carisoma* OR carisoprodat* OR isobamate* OR isomeprobamate* OR isopropylmeprobamate* OR 'mio relax*' OR soma* OR somalgit* OR soprodol* OR vanadomor*)):ti,ab,tn	

Appendix 2: Efficacy Table

Reference Study Design	N	Patient Selection	Treatment Interventions	Results	Adverse Effects
Systematic Reviews/Meta-analysis					
Au, AH et al, 2015[270] SR, MA, RCTs, Placebo, minimal sample size 15 patients SR/MA of 14 studies (through 2012)	N=3521	Acute post-op pain control after 3rd molar surgery	Evaluable patients: Combination analgesics • N=1748 Placebo • N=629 Remaining 1144 received single-dose analgesics (excluded) <u>Codeine containing</u> Acetaminophen 650 mg + Codeine 60 mg (AC650/60) Acetaminophen 600 mg + Codeine 60 mg (AC600/60) Acetaminophen 30 mg + Codeine 30 mg (AC30/30) Acetaminophen 1000 mg + Codeine 30 mg (AC1000/30) <u>Hydrocodone containing</u> Acetaminophen 1000 mg + Hydrocodone 10 mg (AH1000/10) Acetaminophen 500 mg + Hydrocodone 7.5 mg (AH500/7.5) <u>Oxycodone containing</u> Acetaminophen 325 mg + Oxycodone 5 mg (AO) <u>Butalbital containing</u> ASA 325 mg + Butalbital 50 mg + Caffeine 40 mg + Codeine 15 mg (ABCC)	All regimens performed superior to placebo. Meta-analysis found the combination of IO most efficacious • SPID6 (sum of pain intensity @ 6hr): 6.44 • TOTPAR6 (total pain relief @ 6 hr): 9.31 <u>Acetaminophen-containing regimens</u> • No difference was found between AC 650/60 or 600/60 • AC650/60 and AC600/60 were both more efficacious than AC300/30 ○ Adjusted SPID6: 2.1 times higher ○ Adjusted TOTPAR6: 1.6 times higher <u>Aspirin-containing regimens</u> • Adjusted SPID6: 1.08-3.09 • Adjusted TOTPAR: 4.4-6.7 • ABCC > Aspirin + Caffeine > Aspirin + Codeine <u>Ibuprofen-containing regimens</u> • Adjusted SPID6: 1.5-6.44 • Adjusted TOTPAR: 7.0-10.3 ○ IO was at least 1.84 times higher than regimens not containing an opioid (e.g. Ibuprofen + Caffeine)	Reflected usual opioid adverse effects • Overall: Nausea 2.4-55% <u>AH1000/10</u> • Nausea/vomiting 55% • Dizziness 22.4% • Headache 15% • Drowsiness 10.5% <u>AH500/7.5</u> • Nausea 15.25% drowsiness 8.47% <u>AO325/5</u> • Nausea 41% <u>IO400/5</u> • Drowsiness 13.25% <u>Acetaminophen + Codeine combinations</u>: • All AC combinations gave similar and lowest rates of adverse events ○ Nausea 32.7% ○ Headache 18.6% ○ Dizziness 12.4%

Reference Study Design	N	Patient Selection	Treatment Interventions	Results	Adverse Effects
			<u>Ibuprofen containing</u> Ibuprofen 400 mg + Codeine 25.6 mg (IC) Ibuprofen 400 mg + Oxycodone 5 mg (IO) <u>Other nonopioid agents included:</u> Ibuprofen/Caffeine Aspirin/Caffeine Acetaminophen/ibuprofen		

Mkontwana et al, 2015[281]
RCTs
 	
SR, MA of 13 RCTs (16 reports) included but only 8 contributed data to analysis
	N=962	Relief of post-caesarean pain	Opioid vs Placebo
			Non-opioid vs Placebo
			Combination analgesics vs Placebo
			Opioids vs non-opioids
			Opioids vs combination analgesia
				Only 4 trials had a low risk of bias
				All trials were small size with high levels of heterogeneity
				
				<u>Primary Outcome: Adequate pain relief</u>
				No study reported on the primary outcome
				• No conclusion can be made
				
				<u>Primary Outcome: Need for additional pain relief</u>
				No difference between any comparator groups
				• Opioid analgesics vs Placebo
				  ○ RR 0.33, 95% CI 0.06 to 1.92
				• Non-opioid analgesics vs Placebo
				  ○ RR 0.70, 95% CI 0.48-1.01
				• Combination analgesics vs Placebo
				  ○ RR 0.70, 95% CI 0.35 to 1.40
				• Opioid vs Non-opioid analgesics
				  ○ RR 0.51, 95% CI 0.07 to 3.51
				• Opioid vs Combination analgesics
				  ○ RR 0.51, 95% CI 0.07 to 3.51
				• Non-opioid vs Combination analgesics
				  ○ RR 0.87, 95% CI 0.81 to 0.93
				• Subgroup analysis
				  ○ Acetaminophen + Codeine > Placebo
				  ▪ RR 0.44, 95% CI 0.23 to 0.82
				  ○ Acetaminophen + Oxycodone = Placebo
				  ○ Acetaminophen + Propoxyphene = Placebo
					Adverse events more common with Opioids, Non-opioids and Combination analgesics compared with Placebo
					
					Opioid vs Placebo
					• RR 6.58, 95% CI 0.38 to 113.96
					Non-opioid vs Placebo
					• RR 11.12, 95% CI 2.13 to 58.22
					Combinations vs Placebo
					• RR 13.18, 95% CI 2.86 to 60.68
					Opioid vs Non-opioid
					• RR 2.32, 95% CI 1.15 to 4.69
					Opioid vs Combinations
					• RR 6.74, 95% CI 0.39 to 116.79
					Non-opioid vs Combinations
					• Not reported

Moore et al[271]	N≈50,000	Single dose, oral analgesia in moderate to severe postoperative pain	Variety of medications, including 41 analgesic or analgesic combinations Pertinent to this report: <u>Codeine combinations</u>	Primary Outcome Measure (given or calculated): Achievement of 50% maximum pain relief over 4-6 hr compared with placebo (reported as <u>Risk Ratio</u> (RR) and <u>Number Needed to Treat</u> (NNT)	Not presented

Reference Study Design	N	Patient Selection	Treatment Interventions	Results	Adverse Effects
SR, MA of 39 Cochrane Reviews (included ≈460 studies)		Age ≥ 15 years	• Acetaminophen 300 mg + Codeine 30 mg (AC1) • Acetaminophen 600/650 mg + Codeine 60 mg (AC2) • Acetaminophen 800/1000 mg + Codeine 60 mg (AC3) <u>Oxycodone combinations</u> • Acetaminophen 325 mg + Oxycodone 5 mg (AO1) • Acetaminophen 650 mg + Oxycodone 10 mg (AO2) • Acetaminophen 1000 mg + Oxycodone 10 mg (AO3) • Ibuprofen 400 mg + Oxycodone 5 mg (IO) <u>Tramadol combinations</u> • Acetaminophen 650 mg + Tramadol 75 mg (AT)	<u>Studies judged to be reliable¥</u> <u>RR (95% CI)</u> AC2 2.6 (2.2 to 3.2) IO 3.6 (2.6 to 5.1) AO2 3.9 (2.9 to 5.2) AO3 4.9 (3.2 to 7.6) AC3 6.3 (2.9 to 14) <u>NNT (95% CI)</u> AO3 1.8 (1.6 to 2.2) AC3 2.2 (1.8 to 2.9) IO 2.3 (2.0 to 2.8) AO2 2.7 (2.4 to 3.1) AC2 3.9 (3.3 to 4.7) <u>Studies subject to publication bias¥</u> <u>RR (95% CI)</u> AC1 1.9 (1.4 to 2.5) AO1 3.6 (2.1 to 6.3) <u>NNT (95% CI)</u> AO1 5.4 (3.9 to 8.8) AC1 6.9 (4.8 to 12) <u>Tramadol studies from non-Cochrane reviews</u> <u>RR, NNT (95% CI)</u> RR 12 (6.4 to 21) NNT 2.9 (2.5 to 3.5) Mean or median time to remedication • Presented graphically; range: 10 hours to 4 hours ○ AO2 > AO3 > AC3 > AC1	
Alfano et al, 2011 Open reference controlled trial	N=121	Patients undergoing day-surgeries (hallus valgus, hemorrhoidectomy, varicose veins, inguinal hernia repair	Acetaminophen 325 mg + Tramadol 37.5 mg (AT) Or Acetaminophen 500 mg + Codeine 30 mg (AC) Single dose immediately after surgery and four times daily for	Verbal rating scale (VRS) 0-4 (no pain to unbearable pain) Time after surgery (hour) / AC (n=66) / AT (n=55) 1: 0±0 / 0±0 6: 0.72±0.84 / 0.33±0.58* 12: 1.65±1.03 / 1.05±0.95* 24: 2.52±0.86 / 1.40±0.76** 48: 1.71±0.81 / 1.07±0.69**	Adverse events AC 62.1% AT 36.4% *p*=0.008 Most common adverse events • AC: Nausea, vomiting, constipation

Reference Study Design	N	Patient Selection	Treatment Interventions	Results	Adverse Effects
			48 hours. Patients with VRS scores ≥3 received a rescue dose of tramadol 50 mg, subcutaneously	*p<0.01; **p<0.001 % receiving rescue medication 18% 5.5% Quality of life (time to return to standard daily activities, normal nightly rest, appetite, mood, re-ambulation and self-care) • No statistically significant differences were found between groups at any time point	• AT: Nausea, vertigo
Chang et al, 2015[247] PRO, RCT, DB	N=240	Adult patients with acute musculoskeletal extremity pain	Acetaminophen 325 mg + Oxycodone 5 mg (AO) Or Acetaminophen 325 mg + Hydrocodone 5 mg (AH) One tablet every 4 hours Phone contact 24 hours after emergency department discharge to assess pain before most recent dose and decrease in pain score over 2 hours from the most recent dose	Primary Outcome: Mean Numerical rating scale (NRS) 0→10 • Prior to the most recent dosage o AO 7.8 NRS units o AH 7.9 NRS units • Mean decrease in pain score over 2 hours after dose o AO 4.4 NRS units o AH 4.0 NRS units ▪ Difference 0.4 NRS units (95% CI, -0.2 to 1.1 NRS units) ▪ Non-significant with NRS unit difference < 1.3 Both treatments reduced the pain score by ~ 50%	AO 10% higher than AH for nausea and dizziness • Not statistically significant
Chang et al, 2015[282] PRO, RCT, DB	N=240	Adult patients with acute musculoskeletal extremity pain	Acetaminophen 325 mg + Oxycodone 5 mg (AO) Acetaminophen 300 mg + Codeine 30 mg (AC) Two half-tablets every 4 hours as needed (half-tablets due to large tablet size) Phone contact 24 hours after emergency department discharge to assess pain and decrease in pain score over 2 hours for the last treatment dose	Primary Outcome: Mean Numerical Rating Scale (NRS) 0→10 • Prior to the most recent dosage o AO 7.9 NRS units o AC 7.9 NRS units • Mean decrease in pain scores over 2 hours after dose o AO 4.5 NRS units o AC 4.2 NRS units ▪ Difference 0.2 NRS units (95% CI, -0.4 to 0.9) ▪ Non-significant with NRS unit difference < 1.3 Percent achieving 50% pain relief o AO 66% o AC 61% Difference 5% (95% CI, -8% to 17%) Patient satisfaction: Similar between groups	No differences

<table>
<tr><th>Reference
Study Design</th><th>N</th><th>Patient Selection</th><th>Treatment Interventions</th><th>Results</th><th>Adverse Effects</th></tr>
<tr>
<td>Chang et al, 2014[284]

PRO, RCT, DB</td>
<td>N=240</td>
<td>Adult patients with acute musculoskeletal extremity pain discharged from the emergency department with a 3-day course of opioid therapy</td>
<td>Acetaminophen 500 mg + Hydrocodone 5 mg (AH)

Or

Acetaminophen 300 mg + Codeine 30 mg (AC)

One tablet every 4 hours as needed

Phone contact 24 hours after emergency department discharge to assess pain and decrease in pain score over 2 hours for the last treatment dose</td>
<td>Primary outcome: Mean Numerical Rating Scale (NRS) 0→10
• Prior to the most recent dosage
○ AO 7.6 NRS units
○ AC 7.6 NRS units
• Mean decrease in pain scores over 2 hours after dose
○ AO 3.9 NRS units
○ AC 3.5 NRS units
▪ Difference 0.4 NRS units (95% CI, -0.3 to 1.2)
▪ Non-significant with NRS unit difference < 1.3

Percent achieving 50% pain relief: Similar between groups
Patient satisfaction: Similar between groups</td>
<td>No differences</td>
</tr>
<tr>
<td>Corsinovi et al, 2009

6-week

RCT, SB</td>
<td>N=154</td>
<td>Nursing home females (age≥65 years) with severe osteoarthritis-related pain sub-optimally responsive to prior conventional treatments</td>
<td>Acetaminophen 325 mg + Oxycodone 5 mg every 8 hr (AO)

Or

Acetaminophen 500 mg + Codeine 30 mg every 8 hr (AC)

Or

Conventional therapy: NSAIDs, acetaminophen, COX2-inhibitors alone or in combination (CT)</td>
<td>Mean pain reduction in the last week (MeP, NRS)
• All 3 groups vs baseline, p<0.001
○ AO 4.3 ± 1.9
○ AC 3.9 ± 2.1
○ CT 2.1 ±1.2

<table><tr><th>Comparators</th><th>Mean ↓ MeP</th></tr><tr><td>AO vs CT</td><td>p<0.001</td></tr><tr><td>AC vs CT</td><td>p=0.004</td></tr><tr><td>AO vs AC</td><td>p=1.0</td></tr></table>
Mean change in pain at rest from baseline, (RP, NRS)
• all 3 groups from baseline, p<0.001
○ AO 3.0±2.1
○ AC 2.5±1.3
○ CT 1.2±1.2
<table><tr><th>Comparators</th><th>Mean ↓ RP</th></tr><tr><td>AO vs CT</td><td>p<0.001</td></tr><tr><td>AC vs CT</td><td>p=0.001</td></tr><tr><td>AO vs AC</td><td>p=1.0</td></tr></table>
Mean change in pain with movement (PM, NRS)
• all 3 groups from baseline, p<0.001
○ AO 4.4±1.8
○ AC 3.8±1.9
○ CT 2.1±1.7</td>
<td>No difference between groups for adverse events or withdrawals due to adverse events

Discontinuation rates
• AO 19.2%
• AC 30.8%
○ Not statistically significant</td>
</tr>
</table>

<table>
<tr><th>Reference
Study Design</th><th>N</th><th>Patient Selection</th><th>Treatment Interventions</th><th>Results</th><th>Adverse Effects</th></tr>
<tr><td></td><td></td><td></td><td></td><td>
<table>
<tr><th></th><th>Mean ↓ PM</th></tr>
<tr><td>AO vs CT</td><td>p<0.001</td></tr>
<tr><td>AC vs CT</td><td>p=0.002</td></tr>
<tr><td>AO vs AC</td><td>p=0.791</td></tr>
</table>
Depressive symptoms (Beck Depression Inventory-II, BDI-II)
<table>
<tr><th></th><th>Mean improvement in BDI-II</th></tr>
<tr><td>AO vs CT</td><td>p<0.05</td></tr>
<tr><td>AC vs CT</td><td>p=0.04</td></tr>
<tr><td>AO vs AC</td><td>p=1.0</td></tr>
</table>
Functional status (activities of daily living, ADL)
<table>
<tr><th></th><th>Mean improvement in ADL</th></tr>
<tr><td>AO vs CT</td><td>p=0.04</td></tr>
<tr><td>AC vs CT</td><td>p=0.05</td></tr>
<tr><td>AO vs AC</td><td>p=1.0</td></tr>
</table>
Cognitive status (mini mental status exam, MMSE)
No difference between treatments
</td><td></td></tr>
<tr><td>Desjardins et al, 1986

BD, PG, Single-dose study</td><td>N=123</td><td>Adults undergoing outpatient dental surgery (extractions)</td><td>Acetaminophen 300 mg + Codeine 30 mg (AC)
Or
Aspirin 325 mg + Butalbital 50 mg + Caffeine 40 mg + Codeine 30 mg (ABCC)
Or
Placebo

Single-dose when pain intensity required treatment.</td><td>
Measures of analgesic efficacy (mean ± SE)
<table>
<tr><th>Variable</th><th>Placebo</th><th>AC</th><th>ABCC</th></tr>
<tr><td>SPID</td><td>-0.90±0.63</td><td>0.33±0.75</td><td>1.21±0.74</td></tr>
<tr><td>PPID</td><td>0.44±0.12</td><td>0.64±0.12</td><td>0.77±0.13</td></tr>
<tr><td>TPR</td><td>5.10±0.90</td><td>7.82±1.08</td><td>8.37±1.08*</td></tr>
<tr><td>PR</td><td>1.32±0.20</td><td>1.72±0.21</td><td>2.02±0.23*</td></tr>
<tr><td>No. of observations with 50% pain reduction</td><td>1.05±0.27</td><td>1.95±0.39</td><td>1.88±0.33</td></tr>
<tr><td>Time to remedication (min)</td><td>179.7±16.2</td><td>204.9±16.6</td><td>214.5±15.2</td></tr>
<tr><td>Global Assessment</td><td>0.71±0.16</td><td>1.33±0.22*</td><td>1.47±0.20*</td></tr>
</table>
*p<0.05, superior to Placebo

Measures of anxiety and relaxation (mean ± SE)
<table>
<tr><th></th><th>Placebo</th><th>AC</th><th>ABCC</th></tr>
<tr><td>Total anxiety</td><td>10.5±1.0</td><td>7.4±1.1*</td><td>7.5±1.0*</td></tr>
</table>
</td><td>No differences between groups
11 patients reported
Sleepy/drowsy
Nausea
Dizzy
Lightheaded
Headache/neckache</td></tr>
</table>

<table>
<tr><th>Reference
Study Design</th><th>N</th><th>Patient Selection</th><th>Treatment Interventions</th><th>Results</th><th>Adverse Effects</th></tr>
<tr><td></td><td></td><td></td><td></td><td>
<table>
<tr><td>Total relaxation</td><td>7.3±1.0</td><td>9.5±0.9</td><td>9.1±0.8</td></tr>
</table>
*p<0.05, superior to placebo
</td><td></td></tr>
<tr><td>Fricke et al, 2002[275]

DB, Single-dose, PG, placebo- and active-RCT</td><td>N=200</td><td>Adults (16-75 years of age) with at least moderate pain within 5 hours after extraction of at least 2 impacted 3rd molars</td><td>Acetaminophen 325 mg + Tramadol 37.5 mg (AT1)
Or
Acetaminophen 650 mg + Tramadol 75 mg (AT2)
Or
Acetaminophen 650 mg + Hydrocodone 10 mg (AH)
Or
Placebo</td><td>
<u>Primary Endpoints</u>
<table>
<tr><td>TOTPAR

SPID

SPRID</td><td>For all 3 times intervals 0-4 hr, 4-8 hr, 0-8 hr
AT2 vs placebo p≤0.024
AH vs placebo p≤0.024
The 3 active treatments did not differ from each other
Tramadol containing preparations demonstrated a dose-response at each time interval
AT2 > AT1 > placebo
For 0-4 hr only
AT1 > placebo (p≤0.022)</td></tr>
</table>
<u>Secondary Endpoints</u>
Duration of pain relief
AT2 > AH
both significantly longer than placebo
Median time to onset of pain relief
AT regimens ≤34 min
AH 25 min
Time to remedication
Active treatments vs placebo p≤0.001
Patient's overall assessment of study medication
All treatments vs placebo, p<0.001
Supplemental analgesic required, 0-8 hr
AT2 78%
AH 84%
AT1 94.0%
Placebo 94.0%
Supplemental analgesic required 0-2 hr
AT1 54.0%
Placebo 84.0%
</td><td>
Treatment emergent adverse events
Overall 42% of patients
AH 56%
Placebo 48.0%
AT2 34%
AT1 30%
Most Common
Dizziness, headache, nausea, vomiting

Nausea
AT2 18%
AH 36%
p<0.05
Vomiting
AT2 12%
AH 30%
p<0.05
Treatment related adverse events
AH 4%
AT1, AT2 0%
Placebo 10%
</td></tr>
</table>

Reference Study Design	N	Patient Selection	Treatment Interventions	Results	Adverse Effects
Hewitt et al, 2007[274] RCT, MC, DB, PG, OP, active- and placebo controlled	N=603	Adults with acute musculoskeletal pain caused by ankle sprain within previous 48 hours; visual analog pain scale score of at least 50 mm on a 0-100mm scale; pain intensity of moderate-to-severe Urgent care (UC) or emergency department (ED)	Acetaminophen 650 mg + Tramadol 75 mg (AT) Or Acetaminophen 650 mg + Hydrocodone 7.5 mg (AH) Or Placebo First dose administered in UC/ED and continued as an outpatient: One dose up to four times daily for up to 5 days.	For all primary outcome measures of analgesia: TPR during the first 4 hours after drug administration: SPID; SPRID, percent of patients with 30% and 50% pain reduction • Both treatments significantly superior to placebo • Active treatments were not significantly different For primary outcome measures of analgesia • Non-inferiority was demonstrated between active treatment groups ○ Post hoc equivalence/inferiority within 4 hours set as Δ=15% for pooled mean continuous and treatment primary response variables with 95% confidence interval wholly within the ±Δ equivalence interval and included zero. Analgesic efficacy days 1-5 • AH was superior to Placebo for average pain relief and final pain relief • AT was superior to Placebo for average pain relief • Measures of average pain intensity and final pain intensity did not differ between the 3 groups Efficacy failures in the first four hours • AT 6.3% • AH 2.5% • Placebo 11.2% Time to efficacy failures • Significant for AH vs Placebo • Non-significant for AT vs Placebo • Non-significant for AT vs AH	Similar between active groups Most common: somnolence, nausea, dizziness, vomiting Discontinued due to adverse event • AT 10 (5.2%) • AH 9 (4.4%) • Placebo 3 (1.4%)
MacDonald et al, 1966[269] DB, RCT	N=90 (188 pain episodes)	Post-surgical patients with pain	Aspirin 325 mg + Butalbital 50 mg + Caffeine 40 mg + Codeine30 mg (ABCC) Or Acetaminophen 325 mg + Codeine 30 mg (AC) Or Placebo	Pain Relief (patient and physician assessment) • For severe pain ○ AC and ABCC > Placebo, $p<0.001$ ○ ABCC > AC, $p<0.001$ • For moderate pain ○ AC and ABCC > Placebo, $p<0.001$ ○ ABCC = AC • For all pain episodes (moderate and severe) ○ AC and ABCC > Placebo, $p<0.001$ ○ ABCC > AC, $p<0.025$	None noted

Reference Study Design	N	Patient Selection	Treatment Interventions	Results	Adverse Effects
				Severe Pain / Moderate Pain ABCC • Complete relief 59.0% / 77% • Marked relief 33.3% / 13% • Slight relief 5.2% / 0% • No relief 2.5% / 10% AC • Complete relief 31.4% • Marked relief 31.5% / 42% • Slight relief 25.7% / 0% • No relief 11.5% / 3% Placebo • Complete relief 0% / 1% • Marked relief 16% / 63% • Slight relief 39% / 0% • No relief 45% / 25%	
Mullican et al, 2001[272] 4-week, RCT, DB, PG, active-control, double-dummy, MC	N=462	Adults with chronic, nonmalignant low back pain, osteoarthritis pain or both 2:1 randomization AT: AC	Acetaminophen 325 mg + Tramadol 37.5 mg (AT) Or Acetaminophen 300 mg + Codeine 30 mg (AC)	TPR • AT 11.9 vs AC 11.4 ○ Not significantly different SPID • AT 3.8 vs AC 3.3 ○ Not significantly different Pain relief at 30 minutes: Comparable Pain relief 6 hours after dose: Comparable Overall assessment of efficacy by patient and investigators were similar for each treatment group Mean and maximum daily doses were comparable	Types of adverse events comparable AC / AT Somnolence 24% / 17% p=0.05 Constipation 21% / 11% p<0.01 Headache 7% / 11% p=0.08
Palangio et al, 2000[278] 4-week, RCT, PG, DB, MC repeated-dose, active-comparator, Sponsored by Knoll	N=469	Adults with chronic pain: back (45.6%), arthritic (30.9%), other musculoskeletal pain (13.9%) *Less than 5% each with cancer, diabetic neuropathy, postherpetic	Ibuprofen 200 + Hydrocodone 7.5 mg (IH1) Or Ibuprofen 400 mg + Hydrocodone 15 mg (IH2) Or Acetaminophen 600 mg + Codeine 60 mg (AC)	Pain relief scores IH1 1.98±0.87 (p=0.003 vs IH2) IH2 2.25 ±0.89 AC 1.85±0.96 (p<0.001 vs IH2) Mean number of daily doses of medication IH1 3.23±0.76 (p=0.036 vs IH2) IH2 2.94±0.99 AC 3.26±0.75 (p=0.014 vs IH2) Number of daily doses of supplemental analgesics	Number of patients experiencing an adverse event was similar between groups Nausea, dizziness, pruritus, vomiting and sweating • IH2>IH1 (statistically significant)

Reference Study Design	N	Patient Selection	Treatment Interventions	Results	Adverse Effects
Pharmaceuticals		neuropathy, other neurologic or other unclassified chronic pain_	Administered every 6-8 hours as needed for pain	IH1 0.34±0.58 (p=0.021 vs IH2) IH2 0.24±0.49 AC 0.49±0.85 (p=0.010 vs IH2) Global assessment scores • IH2 > AC, p<0.05 weeks 1-4 and overall • IH2>IH1, p<0.05 weeks 1,2 and 4 only For all efficacy variables, IH1 = AC	• AC > IH1, IH2 Diarrhea occurred at a significantly higher rate Dyspepsia • IH1 or AC > IH2 (statistically significant) Discontinuation rates due to adverse events • IH1 14.7% • IH2 26.1% • AC 18.1% ○ AC= IH1, IH2 ○ IH1<IH2, p=0.013 Discontinuation rates to unsatisfactory analgesic response • IH2 1.3% • AC 7.5% p=0.008
Palangio et al, 2002[279] Up to 8-days MC, RCT, DB, PG, repeated-doses Sponsored by Abbott Laboratories	N=147	Adults with moderate to severe acute low back pain	Ibuprofen 200 mg + Hydrocodone 7.5 mg (IH) Or Acetaminophen 325 mg + Oxycodone 5 mg (AO) Dosage regimen: 1 tablet every 4 to 6 hours (MAX 5 tablets daily).	Daily PRS (mean±SD) • IH 2.4±1.06 • AO 2.5±1.01 No difference Daily number of tablets of study medication (mean±SD) • IH 1.8±1.70 • AO 2.20±1.60 No difference Daily number of doses of study medication (mean±SD) • IH 1.80±1.65 • AO 2.10±1.58 No difference Daily mean number of tablets/doses of supplemental analgesic • IH 0.60±1.13 • AO 0.5±0.90 No difference Global evaluation • No difference Short-Form Health Survey (SF-36)	Incidence of Adverse Events • No difference • IH 62.7% • AO 62.5% Most common adverse events related to central nervous and gastrointestinal systems

Reference Study Design	N	Patient Selection	Treatment Interventions	Results	Adverse Effects
				• No difference	

Palangio et al, 2000[280]
 	
RCT, DB, PG, PC single-dose, active-comparator
 	
Sponsored by Knoll Pharmaceutical Company
	N=180	Moderate to severe postoperative obstetric or gynecologic pain	Ibuprofen 400 mg + Hydrocodone 15 mg (IH)
			Or
			Acetaminophen 650 mg + Oxycodone 10 mg (AO)
			Or
			Placebo
				<u>Primary Outcomes</u>
				Mean PRS
				• IH > AO at 5,6 and 8 hr ($p \leq 0.05$)
				  ○ No difference at other time points
				Mean PID
				• IH> AO at 5,6,7 and 8 hr ($p \leq 0.05$)
				  ○ No difference at other time points
				TPR
				• 0→3 hr and 0→ 4 hr: No difference between groups
				• 0→6 hr and 0→8 hr: IH > AO, $p<0.05$
				<u>Secondary Outcomes</u>
				Sum of the PID scores
				• Similar over all time periods
				Median time to onset of analgesia
				• Similar results
				Mean peak PR score
				• Similar results
				Median time to remedication
				• Similar results
				Mean global assessment score
				• Similar results
					Adverse Events
					• IH 18.0%
					• AO 11.9%
					• Placebo 10%

Ziccardi et al, 2000[277] RCT, DB Single-dose study	N=125	Management of postoperative pain following third molar extractions	Ibuprofen 400 mg + Hydrocodone 15 mg (IH) Or Acetaminophen 600 mg + Codeine 60 mg (AC) Or Placebo	Both active treatments were superior to Placebo for all efficacy measures Mean pain relief scores • IH > AC beyond 2 hours, $p<0.05$ Pain intensity differences • IH > AC, numerically only • IH > AC beyond 1.5 hours, $p<0.05$ Time to meaningful pain relief • No difference between active treatments Time to remedication (duration of analgesia) • IH 5.50 hr • AC 3.03 hr (IH > AC, $p<0.001$)	No differences between 3 groups • IH 49% • AC 42.9% • Placebo 22.2% Most common: Somnolence, dizziness, headache, nausea, vomiting, pruritus

Reference Study Design	N	Patient Selection	Treatment Interventions	Results	Adverse Effects
				• Placebo 1.00 hr Mean global evaluation • IH 3.31 > AC 2.78 and Placebo 1.33, $p<0.05$	
Smith et al, 2004[273] MC, RCT, DB, active- and placebo controlled	N=305	Patients with at least moderate post-surgical abdominal and orthopedic pain	Acetaminophen 325 mg + Tramadol 37.5 mg (AT) Or Acetaminophen 300 mg + Codeine 30 mg (AC) Or Placebo Initial 2 tablets, then 1 to 2 tablets every 4 to 6 hours as needed for pain for 6 days (MAX daily dose 8 tablets)	Primary Outcome Measures (first 4 hours) • TOTPAR AT = AC • SPID AT = AC • SP AT = AC For all primary outcome measures • AT > Placebo • AC = Placebo Secondary Outcome Measures (first 4 hours) • Average daily pain relief AC = Placebo • Average daily pain intensity AC = Placebo • Final visit pain intensity AC = Placebo • Final visit pain relief AC = Placebo • AT > AC numerically but not statistically Mean daily dose of active treatment (not statistically different) • AT 4.4 tablets daily • AC 4.3 tablets daily	Discontinuation due to lack of efficacy • AT = AC Adverse effects Constipation • AT 4.1% • AC 10.1% Vomiting • AT 9.2% • AC 14.7% Serious adverse event • AC (1 patient) ○ Constipation Discontinuation due to adverse effect • AT 8.2% • AC 10.1% • Placebo 3.0%

Key: SPID6 measured the difference of the sum of pain intensity score in the first 6 hours post-operatively; Pain intensity score was reported subjectively by the subject on a four-point scale (0 = none; 1 = slight; 2 = moderate; 3 = severe); TOTPAR6 measured pain relief at 6 hours by a categorical rating scale (0 = none; 1 = slight; 2 = moderate; 3 = good; 4 = complete); SPID sum of pain intensity differences; ¥ reliability indicated the number of patients with null effects needed to produce a clinically insignificant effect of worse than 10.

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